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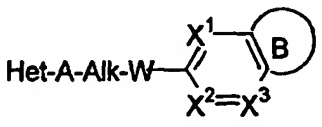
(54) Title: ANTIVIRAL AGENTS



(I)

(57) Abstract: This invention relates to compounds of formula I their salts, and pharmaceutically acceptable derivatives thereof, pharmaceutical compositions comprising these compounds and their use in the treatment of picornavirus infections in mammals as well as novel intermediates useful in the preparation of the compounds of formula I.

ANTIVIRAL AGENTS

This invention relates to antiviral agents, in particular to compounds useful in the treatment of infections caused by Picornaviridae, such as human rhinovirus (HRV) and methods for their preparation. The invention also relates to the use of these compounds in the treatment of picornavirus infections and to intermediates useful in the preparation of these compounds. The compounds of the invention are especially suitable for use in the treatment of HRV and accordingly it will be convenient to describe the invention in connection with these viruses. However it is to be understood that the invention is also applicable to other viruses of the Picornavirus family.

Human rhinovirus are a member of the genus *Rhinovirus* of the picornavirus family and are believed to be responsible for between 40 and 50% of common cold infections. Human rhinoviruses comprise a group of over 100 serotypically distinct viruses and accordingly antiviral activity for multiple serotypes and potency are considered to be equally important factors in drug design.

Two cellular receptors have been identified to which almost all typed HRVs bind. The major group, which comprises 91 of the more than 100 typed serotypes, binds to the intracellular adhesion molecule-1 (ICAM-1) while the minor group, which comprises the rest of typed serotypes with the exception of HRV87, binds to the low density lipoprotein receptor family of proteins.

Another genus of the Picornaviridae family is represented by the Enteroviruses. This genus includes polioviruses 1-3, coxsackieviruses A (23 serotypes) and B(6 serotypes), echoviruses (31 serotypes) and numbered enteroviruses 68-71. The clinical syndromes caused by enteroviruses include poliomyelitis, meningitis, encephalitis, pleurodynia, herpangina, hand foot and mouth disease, conjunctivitis, myocarditis and neonatal diseases such as respiratory illnesses and febrile illnesses.

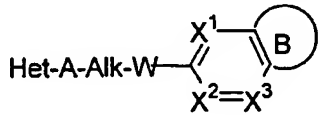
Viruses of the Picornavirus family are characterised by a single stranded (+) RNA genome encapsidated by a protein shell (or capsid) having pseudo icosahedral symmetry. The surface of the capsid contains "canyons" which surround each of the icosahedral fivefold axes and it is believed that the cellular receptors bind to residues on the canyon floor.

A hydrophobic pocket lies underneath the canyon within which a number of antiviral compounds are capable of binding, sometimes with consequential conformational changes. Some of these compounds have been shown to inhibit the uncoating of HRVs and, for some of the major receptor group viruses, inhibition of cell receptor binding has also been demonstrated. It has also been shown that when a compound is bound within the hydrophobic capsid pocket, HRVs are more stable to denaturation by heat or acids.

Examples of antipicorno viral compounds believed to act by binding within the hydrophobic pockets of the picornavirus capsid are described in US Patents 4,857,539, 4,992,433, 5,026,848, 5,051,515, 5,100,893, 5,112,825, 5,070,090, and Australian Patent No. 628172. One compound which has been the subject of recent human clinical trials is ethyl 4-[2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl]-ethoxy]benzoate, otherwise known as "Pirodavir". ("Intranasal Pirodavir (R77,975) Treatment of Rhinovirus Colds" F.G. Hayden, et al., *Antimicrobial Agents and Chemotherapy*, **39**, 290-294, 1995).

A novel class of antiviral compounds has now been discovered which has been found to exhibit particularly favourable antipicornaviral properties.

Accordingly the present invention provides a compound of formula I

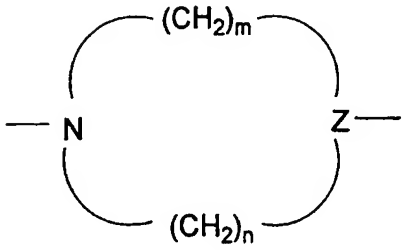


I

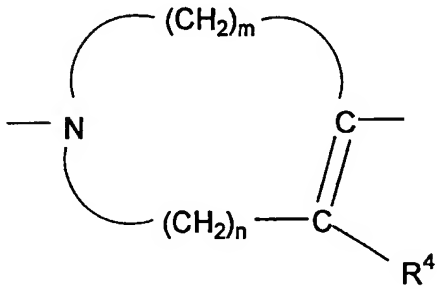
its salts, and pharmaceutically acceptable derivatives thereof where

Het is an optionally substituted 5- or 6-membered monocyclic heterocyclic radical or an optionally substituted 9- or 10-membered bicyclic heterocyclic radical;

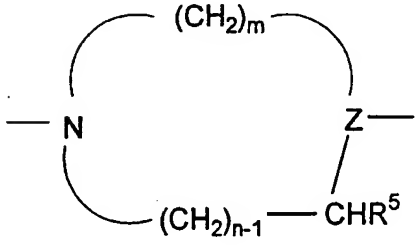
A is O, S, NH, N(C_{1-6}alkyl), CH_2O, a direct bond or a bivalent heterocyclic radical of the formula



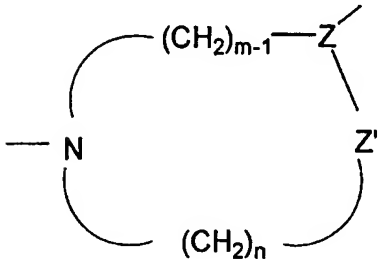
(b-1)



(b-2),



(b-3), or



(b-4)

where one or more of the carbon atoms within the radicals (b-1) to (b-4) may be optionally substituted with C_{1-6}alkyl or two carbon atoms in the radicals (b-1) to (b-4) may be bridged with a C_{2-4}alkylene radical, m and n are each

independently integers of 1 to 4 inclusive with the proviso that the sum of m and n in radicals (b-1) to (b-4) is 3, 4 or 5;

Z is N or CR^6 where R^6 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino;

Z' is O, S, CHR^7 or NR^8 where R^7 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino and R^8 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl; and

R^5 is hydrogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

Alk is C_{1-7}alkylene or a direct bond;

W is O, S, OCH_2, a direct bond or NR^9 where R^9 is hydrogen or C_{1-6}alkyl;

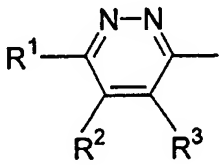
X^1, X^2 and X^3 are each independently selected from N and CR, where R is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy and

B is a five or six membered unsaturated heterocyclic ring, substituted with at least one substituent selected from , R^{10}, OR^{10}, SR^{10} and NR^9R^{10} where R^{10} is C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkenyl, haloC_{1-6}alkenyl, C_{1-6}alkynyl or haloC_{1-6}alkynyl,

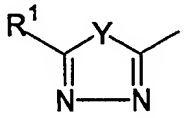
with the proviso that when Alk is a direct bond and A is O, S, CH_2O or a direct bond, then W is not O, S, OCH_2 or a direct bond.

The term "heterocyclic radical" as used herein refers to mono or bicyclic rings or ring systems which include one or more heteroatoms selected from N, S and O. The rings or ring systems generally include 1 to 9 carbon atoms in addition to the heteroatom(s) and may be saturated, unsaturated, aromatic or pseudoaromatic.

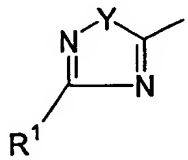
Examples of 5-membered monocyclic heterocycles include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl and examples of 6-membered monocyclic heterocycles include pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl and triazinyl, each of which may be optionally substituted with C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}alkynyl, C_{3-6}alkynyl, halo, hydroxy, mercapto, trifluoromethyl, amino, cyano or mono or di(C_{1-6}alkyl) amino. Examples of 9 and 10-membered bicyclic heterocycles include indolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, isoquinolinyl, quinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, benzotriazinyl and the like, each of which may be optionally substituted with C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}alkynyl, C_{3-6}alkynyl, halo, hydroxy, mercapto, trifluoromethyl, amino, cyano or mono or di(C_{1-6}alkyl) amino. Examples of preferred heterocyclic radicals include (optionally substituted) isoxazoles, isothiazoles, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-oxadiazoles, 1,2,4-thiadiazoles, oxazoles, thiazoles, pyridines, pyridazines, pyrimidines, pyrazines, 1,2,4-triazines, 1,3,5-triazines, benzoxazoles, benzothiazoles, benzisoxazoles, benzisothiazoles, quinolines and quinoxalines. Particular examples of the group Het are radicals of formula (a-1) to (a-14) below:



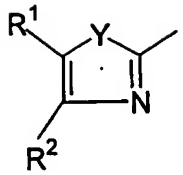
(a-1)



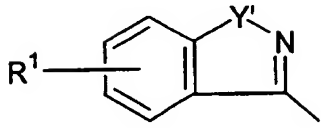
(a-2)



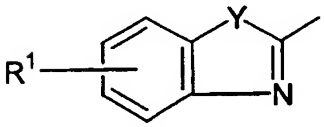
(a-3)



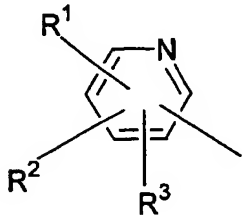
(a-4)



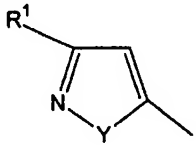
(a-5)



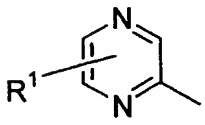
(a-6)



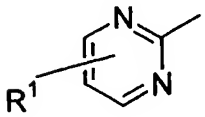
(a-7)



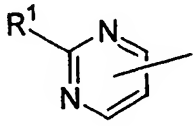
(a-8)



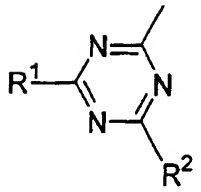
(a-9)



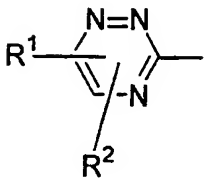
(a-10)



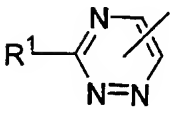
(a-11)



(a-12)



(a-13)



(a-14)

wherein R^1 is hydrogen, C_{1-6} alkyl, halo, hydroxy, mercapto, haloC_{1-6}alkyl, amino, mono or di(C_{1-6}alkyl)amino, cyano, formyl, C_{1-6}alkoxy, hydroxyC_{1-4} alkyl, C_{1-4}alkoxyC_{1-4} alkyl, C_{1-6}haloalkoxy, aryloxy, C_{1-6}alkylthio, arylthio, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, arylsulphinyl, arylsulphonyl, -CH=NO-C_{1-4}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyl or aryl;

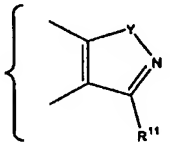
R^2 and R^3 are each independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo or, in radicals (a-1), (a-4), (a-7) and (a-13), R^1 and R^2, or R^2 and R^3 combined may represent a bivalent radical of formula -CH=CH-CH=CH- or $(CH_2)_p$ where p is an integer from 2 to 4;

Y is O or S; and

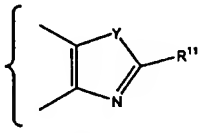
Y' is O, S, SO or SO_2.

The term "unsaturated five or six membered heterocyclic ring" as used herein for ring B refers to a 5 or 6 membered heterocyclic radical fused to the six-membered ring as depicted in Formula I. The ring includes one or more heteroatoms selected from N, S and O and will include 2 to 5 carbon atoms in addition to the heteroatom(s). Two of these

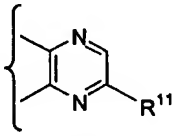
carbon atoms are derived from the six-membered ring to which it is attached. The ring may be partially or fully saturated, and may be aromatic. The ring must contain at least one substituent selected from R^{10}, OR^{10}, SR^{10} and NR^9R^{10}, where R^9 and R^{10} are as defined above. Examples of unsaturated 5-membered heterocyclic rings include oxazole, thiazole, imidazole, 1,2,3-triazole, isoxazole, isothiazole, pyrazole, furan, thiophene and pyrrole, each of which in addition to the defined substituent may be optionally substituted with C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}alkenyl, C_{3-6}alkynyl, halo, hydroxy, mercapto, trifluoromethyl, amino, cyano or mono or di(C_{1-6}alkyl) amino. Examples of unsaturated 6-membered heterocyclic rings include pyridine, pyrimidine, pyrazine, pyridazine and 1,2,4-triazine, each of which in addition to the defined substituent may be optionally substituted with C_{1-6}alkyl, C_{1-6}alkoxy, C_{3-6}alkenyl, C_{3-6}alkynyl, halo, hydroxy, mercapto, trifluoromethyl, amino, cyano or mono or di(C_{1-6}alkyl) amino. Particular examples of unsaturated five or six membered heterocyclic rings include radicals (c-1) to (c-11) below:



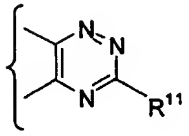
(c-1)



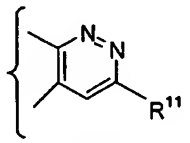
(c-2)



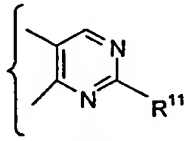
(c-3)



(c-4)



(c-5)



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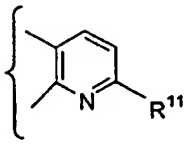

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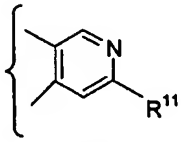
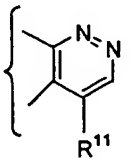
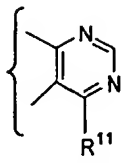


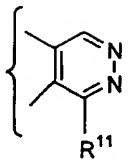
(c-8)



(c-9)



(c-10)



(c-11)

where Y is O, S or NR^9; and R^{11} is R^{10}, OR^{10}, SR^{10} or NR^9R^{10}, where R^9 and R^{10} are as previously defined.

In some preferred embodiments of the invention one or more of the following definitions apply:

Het is a radical of formula (a-1), (a-2) or (a-8);

R^1 is hydrogen, methyl, ethyl, chloro, methoxy or trifluoromethyl;

R^2 and R^3 are each independently hydrogen, chloro or methyl;

Y is O or S;

A is O, NH, NMe, a bond, or a radical of formula (b-1);

Z is CH or N;

Alk is C_{1-6}alkylene or a direct bond;

W is O;

X^1, X^2 and X^3 are CH; and

B is (c-1) or (c-2).

As used herein the term "C_{1-6}alkyl" as used alone or as part of a group such as "di(C_{1-6}alkyl)amino" refers to straight chain, branched or cyclic alkyl groups having from 1 to 6 carbon atoms. Examples of such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, cyclopentyl and cyclohexyl. Similarly C_{1-4} alkyl refers to such groups having from 1 to 4 carbon atoms.

As used herein the term "halo" as used alone or as part of a group such as "C_{3-6}halo alkenyl" refers to fluoro, chloro, bromo and iodo groups.

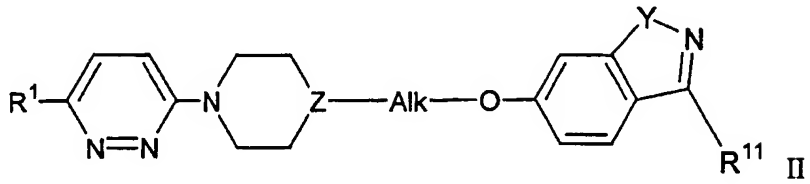
As used herein the terms "C_{1-6}alkoxy" and "C_{1-6}alkyloxy" refer to straight chain or branched alkoxy groups having from 1 to 6 carbon atoms. Examples of C_{1-6}alkoxy include methoxy, ethoxy, n-propoxy, isopropoxy, and the different butoxy isomers.

As used herein the term "C_{3-6}alkenyl" refers to groups formed from C_{3-6} straight chain, branched or cyclic alkenes. Examples of C_{3-6}alkenyl include allyl, 1-methylvinyl, butenyl, iso-butenyl, 3-methyl-2-butenyl, 1-pentenyl, cyclopentenyl, 1-methyl-cyclopentenyl, 1-hexenyl, 3-hexenyl, cyclohexenyl, 1,3-butadienyl, 1-4,pentadienyl, 1,3-cyclopentadienyl, 1,3-hexadienyl, 1,4-hexadienyl, 1,3-cyclohexadienyl and 1,4-cyclohexadienyl.

As used herein the term "C_{3-6}alkynyl" refers to groups formed from C_{3-6} straight chain or branched groups as previously defined which contain a triple bond. Examples of C_{3-6}alkynyl include 2,3-propynyl and 2,3- or 3,4-butynyl.

The term "optionally substituted" as used herein means that a group may include one or more substituents which do not interfere with the binding activity of the compound of formula I. In some instances the substituent may be selected to improve binding. Examples of optional substituents include halo, C_{1-4}alkyl, C_{2-4}alkenyl, C_{2-4}alkynyl, C_{1-4}alkoxy, haloC_{1-4}alkyl, hydroxyC_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkyl, hydroxy, aryl, amino, cyano, mercapto, C_{1-4}alkylamino, C_{1-4}dialkylamino, aryloxy, formyl, C_{1-4}alkylcarbonyl and C_{1-4}alkoxycarbonyl.

A particular group of compounds of the invention has the formula II:



II

wherein:

R^1 is hydrogen, C_{1-4}alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4} alkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

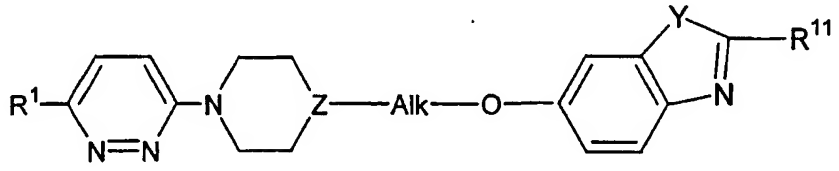
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

Another particular set of compounds of the invention have the formula III:



III

wherein:

R^1 is hydrogen, C_{1-4}alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or

di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4} alkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

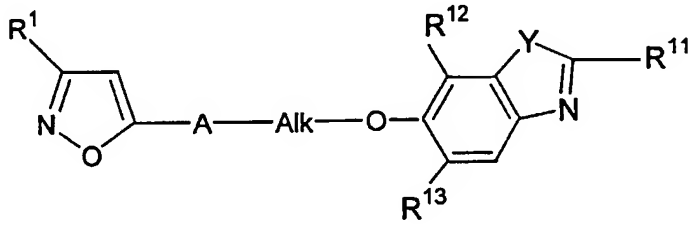
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

Another particular set of compounds of the invention have the formula IV:



IV

wherein:

R^1 is hydrogen, C_{1-4}alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

A is a bond or CH_2O;

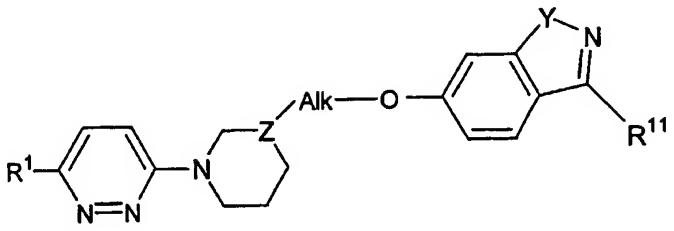
Y is O, S, NH or NMe;

Alk is C_{1-7}alkylene;

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl; and

R^{12} and R^{13} are each independently hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy.

A particular group of compounds of the invention has the formula V



V

wherein:

R^1 is hydrogen, C_{1-4} alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

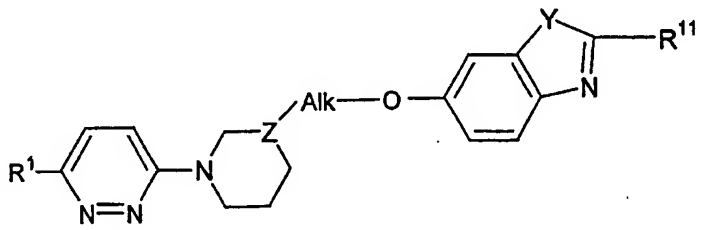
Y is O, S, NH or NMc;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

A particular group of compounds of the invention has the formula VI:



VI

wherein:

R^1 is hydrogen, C_{1-4} alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

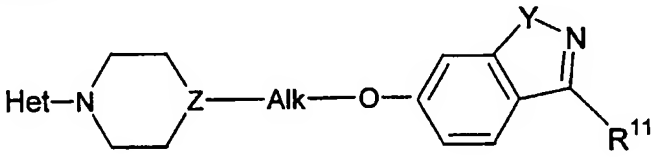
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

A particular group of compounds of the invention has the formula VII



VII

wherein:

Het is pyridyl, pyrazinyl, thiadiazolyl, benzoxazolyl, 1,3,5-triazinyl, pyrimidinyl or quinoxalinyl, each of which may be optionally substituted with 1 to 3 substituents selected from halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy;

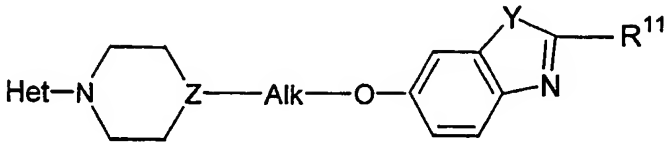
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10} where R^{10} is C_{1-4}alkyl.

A particular group of groups of the invention has the formula VIII:



VIII

wherein:

Het is pyridyl, pyrazinyl, thiadiazolyl, benzoxazolyl, 1,3,5-triazinyl, pyrimidinyl or quinoxalinyl, each of which may be optionally substituted with 1 to 3 substituents selected from halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy;

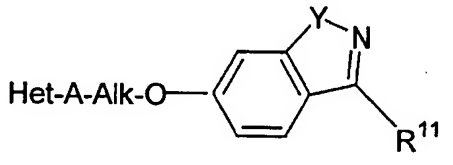
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

Another group of compounds of the invention has the formula IX



IX

wherein:

Het is pyridyl, pyridazinyl, pyrazinyl, thiadiazolyl, benzoxazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, pyrimidinyl or quinoxalinyl, each of which may be optionally substituted with 1 to 3 substituents selected from halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy;

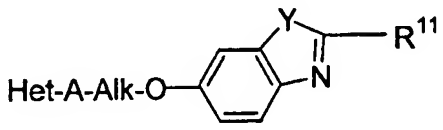
A is a direct bond, O, NH or NMe;

Y is O, S, NH or NMe;

Alk is C_{1-6} alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

Yet another group of compounds of the invention has the formula X:



X

wherein:

Het is pyridyl, pyridazinyl, pyrazinyl, thiadiazolyl, benzoxazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, pyrimidinyl or quinoxalinyl, each of which may be optionally substituted with 1 to 3 substituents selected from halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy;

A is a direct bond, O, NH or NMe;

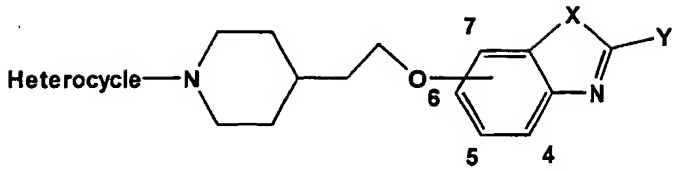
Y is O, S, NH or NMc;

Alk is C_{1-6} alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

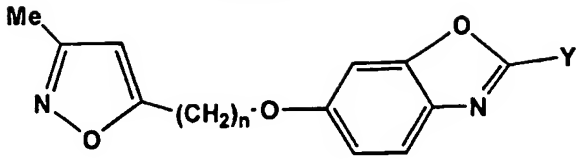
Examples of specific compounds within the scope of the present invention are shown in Tables 1 and 5 below.

Table 1



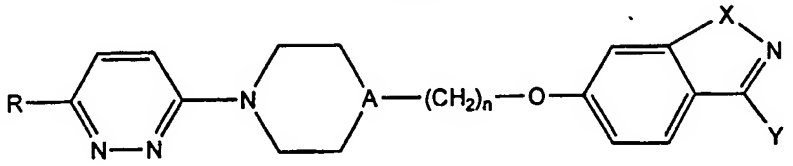
Compd No.	Heterocycle	Position of linkage to benz-azole ring	X Group	Y-Substituent
1	6-Me-3-Pyridazinyl	6	O	Methyl
2	6-Me-3-Pyridazinyl	5	O	Methyl
3	6-Me-3-Pyridazinyl	6	O	Ethyl
4	6-Me-3-Pyridazinyl	6	O	Methylthio
5	6-Me-3-Pyridazinyl	6	O	Ethoxy
6	6-Cl-3-Pyridazinyl	6	O	Methylthio
7	6-Me-3-Pyridazinyl	6	O	Ethylthio
8	6-Cl-3-Pyridazinyl	6	O	Ethylthio
9	5-Methyl-1,3,4-Thiadiazolyl	6	O	Ethylthio
10	5-Methyl-1,3,4-Thiadiazolyl	6	O	Ethoxy
11	6-Me-3-Pyridazinyl	6	O	n-Propoxy
12	6-Me-3-Pyridazinyl	6	O	Methoxy
13	6-Cl-3-Pyridazinyl	6	O	Ethoxy
14	6-Me-3-Pyridazinyl	6	S	Methoxy
15	6-Me-3-Pyridazinyl	6	S	Ethoxy
16	6-Me-3-Pyridazinyl	5/6	NMe	Ethylthio
19	6-Me-3-Pyridazinyl	5	S	Ethylthio
20	6-Me-3-Pyridazinyl	5	S	n-Propoxy
21	6-Me-3-Pyridazinyl	5	S	Ethoxy
22	6-Me-3-Pyridazinyl	5	O	Ethylthio
23	6-Me-3-Pyridazinyl	5	O	Ethoxy
24	6-Me-3-Pyridazinyl	6	S	n-Propylamino
25	6-Me-3-Pyridazinyl	5	NH	Ethylthio
26	6-Me-3-Pyridazinyl	6	O	n-Butyl
27	6-Me-3-Pyridazinyl	6	O	n-Propyl
28	5,6-Me_2-3-Pyridazinyl	6	O	Ethoxy
29	3-Me-1,2,4-Thiadiazol-5-yl	6	O	Ethoxy
30	5,6-Me_2-1,2,4-Triazin-3-yl	6	O	Ethoxy
31	1-Me-Tetrazol-5-yl	6	O	Ethoxy
32	6-Cl-5-Me-3-Pyridazinyl	6	O	Ethoxy
33	5-Me-3-Pyridazinyl	6	O	Ethoxy

Table 2



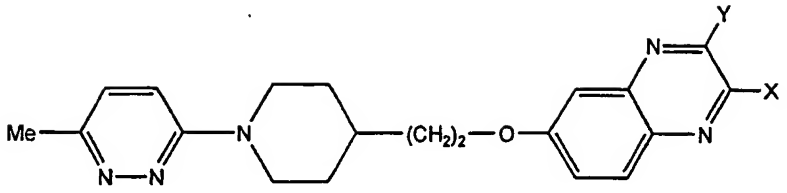
Compound Number	Alkylene chain length n	Y Substituent
17	3	Ethylthio
18	3	Ethoxy
34	5	Ethoxy

Table 3



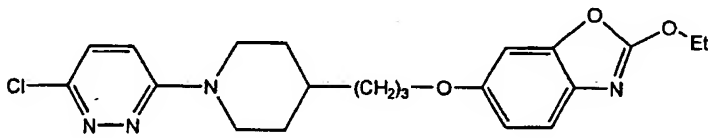
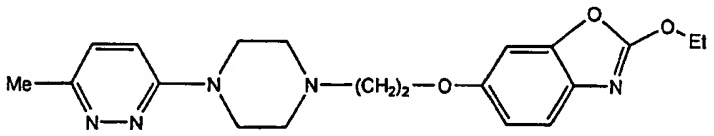
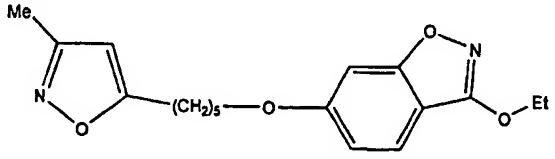
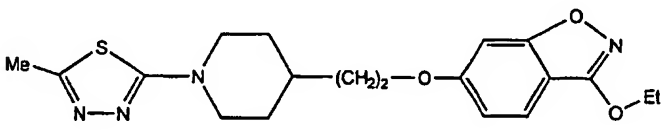
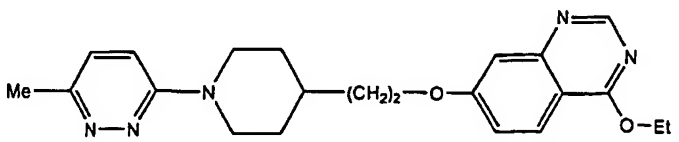
Compound Number	R Substituent	Group A	Alkylene chain length n	Atom X	Group Y
35	Methyl	CH	2	O	Ethoxy
36	Methyl	CH	2	O	Ethyl
37	Chloro	CH	2	O	Ethoxy
38	Methyl	CH	2	O	n-Propoxy
39	Methyl	CH	2	O	n-Propyl
40	Methyl	CH	2	S	Ethoxy
41	Chloro	CH	3	O	Ethoxy
42	Methyl	N	2	O	Ethoxy

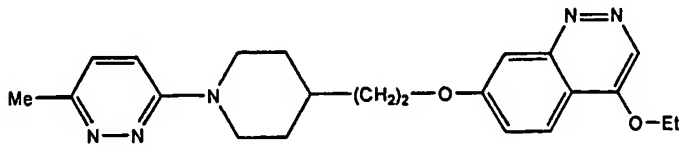
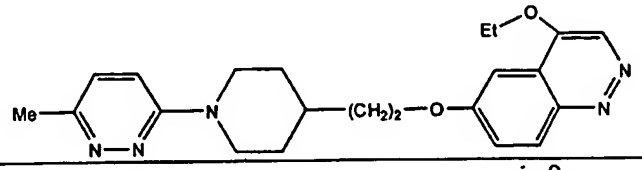
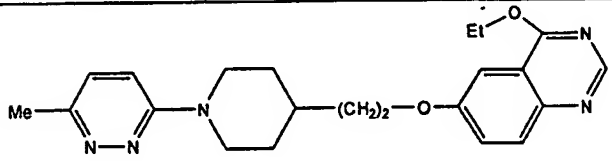
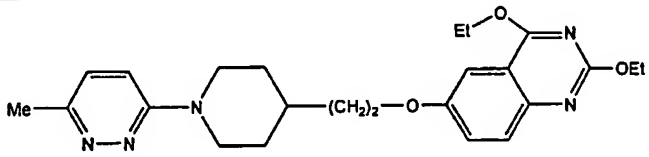
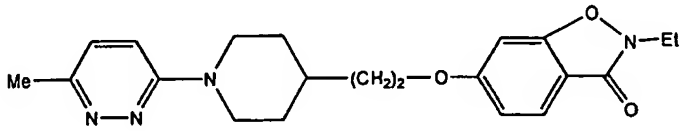
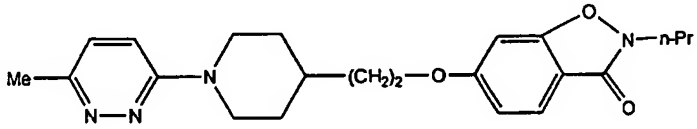
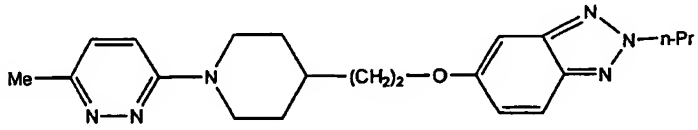
Table 4



Compound Number	X Substituent	Y Substituent
43	Ethoxy	H
44	Chloro	Chloro
45	Ethoxy	Ethoxy
46	H	Ethoxy

Table 5

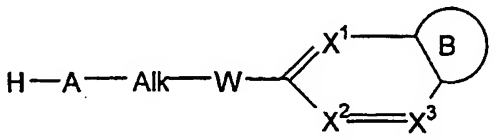
Compound Number	Structure
47	
48	
49	
50	
51	

52	
53	
54	
55	
56	
57	
58	

The compounds of the present invention may be prepared using methods analogous to those described in the prior art. For example, compounds in which the Het radical is of formula (a-1) may be prepared using methodology analogous to the processes described in US Patents 4,992,433, 5,112,825 and 5,100,893. Similarly, compounds in which Het is (a-2), (a-3), (a-4), (a-5) or (a-6) may be prepared using methodology similar to that described in US Patent 5,070,090 and Australian patent No. 629172, and compounds in which Het is

(a-7) or (a-8) may be prepared in accordance with methodology similar to that described in US Patent 5,364,865.

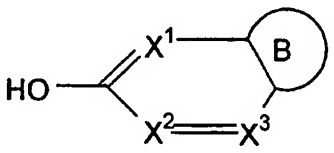
In one method the compounds of the present invention are prepared via an intermediate of formula XI:



XI

where A, Alk, W, Ar, X^1, X^2 , X^3 and B are as described above.

This intermediate may be prepared using methodology similar to that described in US Patent 5,231,184. In one example intermediates of formula XI, when W is O, are prepared by the reaction of compounds of the formula P-A-Alk-OH or P-A-Alk-L with hydroxy aromatic compounds of formula XII.



XII

where Ar, X^1, X^2, X^3 and B are as defined above, P is H or a protecting group, and L is a leaving group. Removal of the protecting group P in the reaction product affords the reactive intermediates of formula XI.

Examples of suitable protecting groups P in compounds of formula P-A-Alk-OH or P-A-Alk-L include benzyl or acyl moieties which can be introduced and removed by standard methods (see "Protective Groups in Organic Synthesis" Theodora Green, Wiley Interscience, 1981).

The intermediate of formula XI may be reacted with a compound of formula Het-L, where Het is as defined above and L is a suitable leaving group to afford a compound of formula I. Where this reaction is an N-alkylation reaction it can be conducted using procedures known to the art, such as under the conditions described in US Patent 5,231,184 for performing analogous N-alkylations. In performing the reaction described above it may be necessary to protect one or more substituents on groups such as X^1, X^2, X^3 or B.

Some of the intermediates of formula XI and XII are novel and represent a further aspect of the present invention.

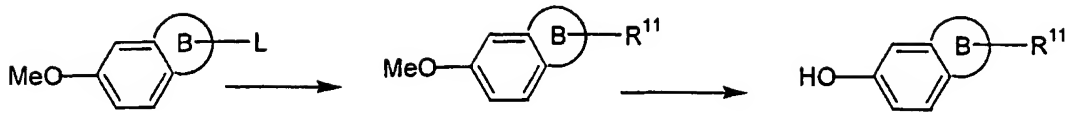
Examples of suitable leaving groups include halogen, such as fluoro, chloro, bromo and iodo, and halogen-like groups such as p-toluenesulphonyloxy and methanesulphonyloxy.

An additional method of preparing certain compounds of the invention of formula Ia (Compounds for formula I where W = O) involves condensing a compound of formula XIII with a suitable precursor of formula XII:

(XII) (XIII) (Ia)

using Mitsunobu Reaction conditions (see Chemical Syntheses, Vol. 42, p 335, 1992) and where Het, A, Alk, X^1, X^2, X^3 and B are as defined for formula I.

Intermediates of formula XII may often be prepared from protected forms of the hydroxy compound. For example compounds of formula XII wherein X^1-X^3 are CH (hereinafter referred to as compounds of formula (XIIa)) can be made from the corresponding compounds which have an alkoxy or benzyloxy substituent which can be converted to OH by routine deprotection reagents including HBr or BBr_3.



(XIIc) (XIIb) (XIIa)

The chemical literature contains many references to the preparation of compounds of formula (XIIb) including for example US Patent 5,919,807 and J. Org. Chem., **61**, 3289 (1996). Compounds of formula (XIIb) can generally be prepared from the corresponding compounds (XIIc) which have a leaving group L available for displacement by R^{11} when R^{11} is OR^{10}, SR^{10} or NR^9R^{10}. There are several references in the literature to the preparation of examples of compounds of general formula (XIIc), for example in US Patents 5,919,807, 5,747,498 and J. Med. Chem., **24**, 93 (1981).

Several references, including US Patents 5,112,825 and 5,242,924 describe methods for the preparation of various compounds of formula XIII.

The compounds of the present invention are useful in the prevention or treatment of picornoviral infections in mammals, particularly humans.

Accordingly in a further aspect the invention provides a method for the treatment or prophylaxis of a picornaviral infection in a mammal including the step of administering an effective amount of a compound of formula I.

The picornavirus infection may be caused by any virus of the family Picornaviridae. Representative family members include human rhinoviruses, polioviruses, enteroviruses including coxsackieviruses and echoviruses, hepatovirus, cardioviruses, apthovirus, hepatitis A and other picornaviruses not yet assigned to a particular genus, including one or more of the serotypes of these viruses. Preferably the invention is used in the prevention or treatment of infection caused by one or more serotypes of rhinovirus.

Without wishing to be limited by theory it is believed that the heteroatoms in the fused heterocyclic moiety of the compound of formula I may be involved in hydrogen bonding

with an asparagine residue generally present near the opening of the hydrophobic pocket and that this interaction enhances the binding of the compounds in the capsid pocket, relative to the prior art compounds. It is further believed that the fused heterocyclic moiety may be more resistant to hydrolysis and esterase activity than the ester bond of pirodavir, and that this may allow more flexibility in the methods of administration of the compound to the site of activity, than available for readily hydrolysable pirodavir. In particular it may allow oral administration of the compounds or reduce metabolism in the nasal mucosa following topical administration.

The salts of the compound of formula I are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts. The pharmaceutically acceptable salts may include conventional non-toxic salts or quartenary ammonium salts of these compounds, which may be formed, e.g. from organic or inorganic acids or bases. Examples of such acid addition salts include, but are not limited to, those formed with pharmaceutically acceptable acids such as acetic, propionic, citric, lactic, methanesulphonic, toluenesulphonic, benzenesulphonic, salicyclic, ascorbic, hydrochloric, orthophosphoric, sulphuric and hydrobromic acids. Base salts includes, but is not limited to, those formed with pharmaceutically acceptable cations, such as sodium, potassium, lithium, calcium magnesium, ammonium and alkylammonium. Also, basic nitrogen-containing groups may be quaternised with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others.

The compounds of the invention may be in crystalline form or as solvates (e.g. hydrates) and it is intended that both forms are within the scope of the present invention. Methods of solvation are generally known within the art.

Pharmaceutically acceptable derivatives may include any pharmaceutically acceptable salt, hydrate or any other compound or prodrug which, upon administration to a subject, is

capable of providing (directly or indirectly) a compound of formula I or an antivirally active metabolite or residue thereof.

Any compound that is a prodrug of a compound of formula I is within the scope and spirit of the invention. The term "pro-drug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where a free hydroxy group is converted into an ester derivative or a ring nitrogen atom is converted to an N-oxide. Examples of ester derivatives include alkyl esters, phosphate esters and those formed from amino acids, preferably valine.

It will be appreciated that some derivatives of the compound of formula I may have an asymmetric centre, and therefore are capable of existing in more than one stereoisomeric form. The invention extends to each of these forms individually and to mixtures thereof, including racemates. The isomers may be separated conventionally by chromatographic methods or using a resolving agent. Alternatively the individual isomers may be prepared by asymmetric synthesis using chiral intermediates.

The invention also provides the use of a compound of formula I in the manufacture of a medicament for the treatment or prophylaxis of picornavirus infection.

While it is possible that, for use in therapy, a compound of the invention may be administered as the neat chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

In view of the general lipophilic nature of the compounds they are particularly suitable to oral forms of administration, however other forms of administration are also envisaged.

The invention thus further provides pharmaceutical formulations comprising a compound of the invention or a pharmaceutically acceptable salt or derivative thereof together with one or more pharmaceutically acceptable carriers therefor and, optionally, other therapeutic

and/or prophylactic ingredients. The carrier(s) must be acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compounds of this invention may also be useful in combination with known anti-viral or anti-retroviral agents or other pharmaceuticals used in the treatment of viral infections. Representative examples of these additional pharmaceuticals include immunomodulators, immunostimulants, antibiotics and anti-inflammatory agents. Exemplary anti-viral agents include zanamivir, rimantidine, amantidine, ribavirin, AZT, 3TC, (-) FTC, acyclovir, famciclovir, penciclovir, ddI, ddC, ganciclovir, saquanivir, loviride, other non-nucleotide reverse transcriptase (RT) inhibitors and protease inhibitors, antiviral and antireceptor antibodies and receptor analogues, such as ICAM-1. Exemplary immunomodulators and immunostimulants include various interleukins, cytokines and antibody preparations. Exemplary antibiotics includes antifungal agents and antibacterial agents. Exemplary anti-inflammatory agents include glucocorticoids and non-steroidal anti-inflammatory compounds.

Pharmaceutical formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation. The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to

two hundred (200) milligrams, per tablet, are accordingly suitable representative unit dosage forms. The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The compounds according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilizing and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump. To improve nasal delivery and retention the compounds according to the invention may be encapsulated with cyclodextrins, or formulated with their agents expected to enhance delivery and retention in the nasal mucosa.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas.

The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP).

Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 1 to 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Liquids or powders for intranasal administration, tablets or capsules for oral administration and liquids for intravenous administration are preferred compositions.

The invention will now be described with reference to the following examples which illustrate some preferred aspects of the present invention. However it is to be understood that the particularity of the following description of the invention is not to supersede the generality of the preceding description of the invention.

EXAMPLES

Example 1 Preparation of 6-{2-[1-(6-Methyl-3-pyridazinyl)-4-piperidinyl]ethoxy}-2-methylthiobenzoxazole (Compound 4 from Table 1)

(a) Preparation of 2-mercapto-6-hydroxybenzoxazole (see also J. Org.Chem., **19**, 758)

A mixture of aminoresorcinol hydrochloride (1.1 g), potassium ethyl xanthate (1.2 g) and potassium carbonate (1.0 g) was dissolved in ethanol/water (1:1, 20ml) and (under an argon balloon) heated under reflux for 3 hours. The pale yellow solution was cooled to RT and then acetic acid (2 ml) was added to make the solution slightly acidic (gas evolution). A cream precipitate soon formed and the sealed flask was kept in the fridge overnight. The cream solid was collected by filtration and the damp product (0.9 g) was used immediately in the next step.

(b) Preparation of 6-hydroxy-2-methylthiobenzoxazole

A mixture of 6-hydroxy-2-mercaptobenzoxazole (165mg), sodium bicarbonate (84mg) and dimethyl sulfate (94µl) was dissolved in water (2 ml) with stirring and under an argon atmosphere. The reaction mixture was stirred at RT overnight and HPLC showed that all starting material was gone. The reaction mixture was evaporated to dryness to give a dark brown solid (one can also extract the reaction mixture with chloroform to give the crude product). Chromatography on silica gel using 10% ethyl acetate/hexane gave the pure product as a near-white crystalline solid (45mg, 25%).

(c) Preparation of 2-Methylthio-6-[N-(6-methyl-3-pyridazinyl)piperidinyl-4-ethoxy]benzoxazole (Compound 4)

A mixture of 6-hydroxy-2-methylthiobenzoxazole (100mg), 3-[4-(2-chloroethyl)-1-piperidinyl]-6-methylpyridazine (130mg) and potassium carbonate (100mg) was heated and stirred in DMF (3ml) at 90-100° under argon for 20hr. Tlc showed that the reaction was virtually complete and the DMF was removed under reduced pressure and the residue

was partitioned between water and chloroform. The chloroform extracts were evaporated and the residue was chromatographed on silica/chloroform to give the product as a pale cream solid (110mg, 50%). The ^{1}H nmr spectrum is summarised in Table 6 below.

Example 2 Preparation of 2-Ethoxy-6-{2-[N-(6-methyl-3-pyridazinyl)piperidinyl]-4-ethoxy}benzoxazole (Compound No 5)

Sodium metal (100mg) was dissolved in ethanol (5ml) and the solution was added to a solution of the methylthiobenzoxazole (compound No. 4) (74mg) in THF (2ml). The resultant solution was stirred at RT for 24hr when hplc indicated that all starting material had disappeared. The reaction mixture was evaporated to dryness and the residue was partitioned between water and dichloromethane. The crude organic product was purified by chromatography on silica/CH_2Cl_2 to give Compound No. 5 as a pale cream solid (46mg). The ^{1}H nmr and MS data are recorded in Table 6 below.

Example 3

Compounds No 1, 2, 3, 6, 7, 8, 9, 17, 19, 22, 25, 26, 27 were prepared by reacting the appropriate Het-A-Alk-Cl or Het-A-Alk-OH with the required 2-substituted 5- or 6-hydroxybenz-azole (benzoxazole, benzothiazole or benzimidazole) following similar conditions to those described in Example 1 part (c). The ^{1}H nmr and/or MS data are recorded in Table 6 below.

Example 4

The 2-alkoxybenz-azole derivatives, Compounds No 10, 11, 12, 13, 14, 15, 18, 20, 21, 23 were prepared from the corresponding 2-methylthio or 2-ethylthiobenzoxazole or benzothiazole by reaction with the appropriate sodium alkoxide following essentially the same conditions as described in Example 2. The ^{1}H nmr and/or MS data are recorded in Table 6 below.

Example 5 Preparation of a mixture of 2-Ethylthio-3-Methyl-6-{2-[N-(6-methyl-3-pyridazinyl)piperidinyl]-4-ethoxy}benzimidazole and 2-Ethylthio-3-Methyl-5-{2-[N-(6-methyl-3-pyridazinyl)piperidinyl]-4-ethoxy}benzimidazole (Compound No 16)

Methylation of 2-ethylthio-5-hydroxybenzimidazole gave an approximately 1:1 mixture of 2-ethylthio-3-methyl-5-hydroxybenzimidazole and 2-ethylthio-3-methyl-6-hydroxybenzimidazole which could not be easily separated. Reaction of this mixture of hydroxy compounds with 3-[4-(2-chloroethyl)-1-piperidinyl]-6-methylpyridazine, following the method described in Example 1, gave a 1:1 mixture of isomeric products (Compound No 16).

Example 6 Preparation of 6-{2-[1-(6-Methyl-3-pyridazinyl)-4-piperidinyl]ethoxy}-3-ethoxy-1,2-benzisoxazole (Compound 35 from Table 3)

(a) Preparation of 2-hydroxy-4-methoxybenzohydroxamic acid

According to literature procedure *Chem. Ber. 100, 954-960 (1967)*

An hydroxylamine solution was prepared by addition of aqueous sodium hydroxide (393 mg, 9.82 mmol)/water (1.6 ml) to a stirred solution of hydroxylamine hydrochloride (292 mg, 4.21 mmol) in water (3.5 ml). Immediately slowly added a solution of methyl 2-hydroxy-4-methoxybenzoate (511 mg, 2.81 mmol) in 1,4-dioxane (1.5 ml). The resulting reaction mixture was stirred at room temperature for 18 hours, under an argon atmosphere. The reaction mixture was concentrated on a rotary evaporator to half the original volume, and the product precipitated by addition of concentrated hydrochloric acid, keeping flask cool in an ice bath. Filtered the suspension to give 2-hydroxy-4-methoxybenzohydroxamic acid (476mg, 92%) as a pale brown solid.

^{1}H nmr spectrum ($CDCl_3$) δ (ppm): 3.72 (s, 3H); 6.36 (m, 2H); 7.41 (d, 1H).

(b) Preparation of 3-hydroxy-6-methoxy-1,2-benzisoxazole

A solution of carbonyl diimidazole (1.07g, 6.57mmol) in anhydrous THF (8ml) was added to a stirred boiling solution of the hydroxamic acid (602mg, 3.29mmol) in THF (6ml). The resulting solution was heated at reflux for approx. 8-10 hours, then allowed to cool to room temperature and stirred overnight under an argon atmosphere. Thin layer chromatography (tlc) (silica; 1:1 hexane/ethyl acetate) showed minimal starting material and new non polar material. The solution was evaporated on a rotary evaporator to give an orange coloured oil. Water (6ml) was added, and contents cooled (ice bath) and acidified to pH 2 with concentrated hydrochloric acid. The crude, damp 3-hydroxy-6-methoxy-1,2-benzisoxazole precipitated as a cream orange solid (645mg).

^{1}H nmr spectrum ($CDCl_3$) δ (ppm): 3.82 (s, 3H); 6.73 (fd, 1H); 6.80 (dd, 1H); 7.52 (d, 1H).

LCMS (ESI) 166 $(M+1)^+$

(c) Preparation of 3-ethoxy-6-methoxy-1,2-benzisoxazole

Benzisoxazole from part (b) (193mg, 1.17mmol), ethanol (75µl, 1.29mmol) and triphenylphosphine (460mg, 1.75mmol) were dissolved in anhydrous THF (4ml) and cooled (0°). Diisopropylazodicarboxylate (345µl, 1.75mmol) was added slowly and after 10-15min the reaction flask was removed from the ice bath and the reaction mixture was stirred at room temperature overnight under an argon atmosphere. The solution was evaporated to dryness and the residue pre-absorbed onto silica, and chromatographed on silica (19g); eluent: hexane (300ml), 10-30% ethyl acetate/hexane to give 3-ethoxy-6-methoxy-1,2-benzisoxazole (101mg, 44%) as white crystals.

^{1}H nmr spectrum ($CDCl_3$) δ (ppm): 1.50 (t, 3H); 3.87 (s, 3H); 4.47 (q, 2H); 6.86 (m, 2H), 7.47 (d, 1H).

LCMS (ESI) 194 $(M+1)^+$

(d) Preparation of 3-ethoxy-6-hydroxy-1,2-benzisoxazole

Boron tribromide (1.0M solution in dichloromethane; 1.39ml, 1.39mmol) was added to a stirred, -78°cooled solution of benzisoxazole from part © (179mg, 928μmol) in dichloromethane (4ml) under an argon atmosphere. The reaction mixture was gradually warmed to room temperature over approx. 2 hours, and stirred overnight. Tlc (silica, 2:1 hexane/ethyl acetate) showed new polar material as well as unreacted starting material. The reaction was worked up by adding water (5ml) and ice. The aqueous phase was neutralised by addition of saturated $NaHCO_3$ solution, and saturated with NaCl. The aqueous phase was extracted into dichloromethane (3 x 60ml), then the organic extracts combined and washed with brine (10ml) and dried ($NaSO_4$). The product was purified by chromatography on silica (18g; eluent 2.5%, 5%, then 15% ethyl acetate/hexane). The first compound to elute was unreacted 3-ethoxy-6-methoxy-1,2-benzisoxazole, (46mg), followed by 3-ethoxy-6-hydroxy-1,2-benzisoxazole 108mg (65%).

^{1}H nmr spectrum ($CDCl_3$) δ (ppm): 1.45 (t, 3H); 4.40 (q, 2H); 6.74 (m, 2H); 7.38 (m, 1H).

LCMS (ESI) 180 $(M+1)^+$

(e) Preparation of Compound 35

A mixture of 2-[-1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethanol (42mg, 188μmol), benzisoxazole from part (d) (28mg, 156μmol) and polymer-supported triphenylphosphine (145mg, 234μmol) in anhydrous THF (3ml) was cooled (0°) and stirred under an argon atmosphere. Neat diisopropylazodicarboxylate (46μml, 234μmol) was added slowly and the reaction mixture was allowed to warm to room temperature and stir overnight. The reaction mixture was filtered, then pre-adsorbed onto silica and chromatographed on silica (approx. 5g); using firstly 2:1 hexane/ethyl acetate as eluent, then gradually increased to 70% ethyl acetate/hexane to afford Compound 35 (44mg; 73%) as a white powder. The ^{1}H nmr and MS data are recorded in Table 6 below.

Example 7

Compounds No 36, 37, 38, 39, 40, 41, 42, 49, 50, 56 and 57 were prepared by reacting the appropriate Het-A-Alk-Cl or Het-A-Alk-OH with the required 3-substituted 6-hydroxy-1,2-benzisoxazole (or 1,2-benzisothiazole) following similar conditions to those described in Example 6. The ^{1}H nmr and/or MS data are recorded in Table 6 below.

Example 8

The n-propylaminobenzothiazole derivative, Compound No 24, was prepared from the corresponding 2-methoxy-benzothiazole (Compound 14) by heating with excess n-propylamine. The ^{1}H nmr and/or MS data are recorded in Table 6 below.

Example 9 Preparation of 2-Ethoxy-6-{2-[N-(5,6-dimethyl-3-pyridazinyl)piperidinyl]-4-ethoxy}benzoxazole (Compound No 28)

(a) Preparation of 2-ethoxy-6-hydroxybenzoxazole

A mixture of equivalent amounts of 4-aminoresorcinol hydrochloride and anhydrous sodium acetate in anhydrous ethanol was stirred for 16 hours at room temperature with a slight excess of tetraethyl orthocarbonate to give 2-ethoxy-6-hydroxybenzoxazole in 60% yield.

(b) Reaction of 2-ethoxy-6-hydroxybenzoxazole with 2-[-1-(5,6-dimethyl-3-pyridazinyl)-4-piperidinyl]ethanol was carried out using a Mitsunobu coupling and similar conditions to those described in Example 6 part (e). The ^{1}H nmr and/or MS data for Compound 28 are recorded in Table 6 below.

Example 10

Compounds No 29, 30, 31, 32, 33, 34, 47 and 48 were prepared by reacting the appropriate Het-A-Alk-Cl or Het-A-Alk-OH with 2-ethoxy-6-hydroxybenzoxazole following similar conditions to those described in Example 1, part © or Example 6 part (e). The ^{1}H nmr and/or MS data are recorded in Table 6 below.

Example 11 Preparation of 6-{2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethoxy}-4-ethoxy-cinnoline (Compound 53 from Table 5)

(a) Preparation of 4-chloro-6-methoxycinnoline

6-Methoxy-4-hydroxycinnoline (Osborn, A.R. and Schofield, K. J. Chem. Soc., **1955**, 2100) was prepared from 2-amino-5-methoxyacetophenone by diazotisation.

Phosphorous oxychloride (5ml) was added to a mix of dimethylaniline (157mg, 1.3mmol) and 6-methoxy-4-hydroxycinnoline (208mg, 1.2mmol). The reaction was heated at reflux for 15min, then cooled and concentrated under vacuum. The residue was partitioned between chloroform (100ml) and water (30ml), then the organic layer was washed with brine and dried (Na_2SO_4). Chromatography of the residue adsorbed onto silica gel (3g) on silica gel (15g) eluent CH_2Cl_2 to 10% Ethylacetate/ CH_2Cl_2 gave 6-methoxy-4-chlorocinnoline (135mg, 0.7mmol) in 59% yield as white yellow solid. δ_H ($CDCl_3$) = 4.03 (s, 3H); 7.28 (d, 1H); 7.51 (dd, 1H); 8.41 (d, 1H) and 9.22 (br s, 1H). MS (ESI) $(M+H)^+$ 195.

(b) Preparation of 4-chloro-6-hydroxycinnoline

A solution of 6-methoxy-4-chlorocinnoline (135mg, 0.7mmol) in toluene (7ml) was added to a stirred suspension of aluminium trichloride (231mg, 1.73mmol) in toluene (7ml) and the red brown suspension was refluxed for 1hr. The solvent was removed under vacuum and the residue was partitioned between water (20ml) and 10%ethanol/chloroform

(2x100ml). The organic layer was washed with brine and dried (Na_2SO_4). Removal of the solvent under vacuum gave 6-hydroxy-4-chlorocinnoline (154mg) as a single component by TLC (1:1 ethylacetate/hexanes). δ_H (CD_3OD) = 7.33 (d, 1H); 7.56 (dd, 1H); 8.32 (d, 1H) and 9.15 (br s 1H). MS (ESI) $(M+H)^+$ 181.

(c) Preparation of 6-{2-[(1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethoxy)}-4-chlorocinnoline

A solution of DIAD (42mg, 0.21mmol) in THF (0.4ml) was added slowly to a suspension containing 6-hydroxy-4-chlorocinnoline (30mg, 0.17mmol), triphenylphosphine (65mg, 0.25mmol) and 1-(6-methyl-3-pyridazinyl)-4-(2-hydroxyethyl)-piperidine (40mg, 0.18mmol) in THF (5ml) and the suspension cleared. The reaction was left to stir overnight, then the reaction was adsorbed onto silica (1.5g) and chromatography on silica gel (8g) eluent ethylacetate gave the product (50mg, 0.13mmol) in 72% yield. ^1H nmr δ_H (CD_3OD) = 1.35 (m, 2H); 1.9 (m, 5H); 2.46 (s, 3H); 2.95 (m, 2H); 4.34 (m, 4H); 7.19 (d, 1H); 7.26 (d, 1H); 7.42 (d, 1H); 7.64 (dd, 1H); 8.34 (d 1H) and 9.24 (br s 1H).
MS (ESI) $(M+H)^+$ 384.

(d) Preparation of Compound No 53

A solution of sodium ethoxide (0.3mmol) in ethanol (0.15ml) was added dropwise to a solution of the above (part c) 4-chlorocinnoline (23mg, 60μmol) in dry ethanol (3ml) and the reaction was allowed to stir for 2hr. The reaction was quenched with saturated ammonium chloride/brine (1ml) and solvents removed under vacuum. The residue was partitioned between brine (5ml) and 5%ethanol/ethylacetate (2x30ml), dried (Na_2SO_4) and adsorbed onto silica (1g) under vacuum. Chromatography on silica gel (8g) eluent 5%methanol/ethylacetate gave Compound No 53 (15mg, 38μmol) in 63% yield.

Example 12 Preparation of 7-{2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethoxy}-4-ethoxy-cinnoline (Compound 52 from Table 5)

4-Hydroxy-7-methoxy-cinnoline (Osborn, A.R. and Schofield, K. J. Chem. Soc. (1955) 2100) was prepared following a similar method to that described in Example 11 for the 6-isomer. This compound was converted to Compound 52 in a similar manner to that described in Example 11 for the 6-isomer. The ^{1}H nmr and MS data are recorded in Table 6 below

Example 13 Preparation of 7-{2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethoxy}-4-ethoxy-quinazoline (Compound 51 from Table 5)

(a) Synthesis of 7-nitroquinazolin-4-one

A mixture of 4–nitroanthranilic acid (2.17g, 11.91mmol) and formamide (1.5mL, 38.43mmol) was heated at 165°C for 4 hours. The warm reaction mixture was poured into ice/water (30mL) and the resulting precipitate was collected via filtration, to give an orange solid (2.16g, 95% yield) which was dried over P_2O_5. This was used without further purification.

^{1}H nmr; 8.24 (d, 1H), 8.32 (s, 1H), 8.34 (s, 1H), 8.35 (d, 1H).

(b) Synthesis of 7-Aminoquinazolin-4-one

Pd/C (100mg) was added as a single portion to a degassed and flushed (3 x Ar) suspension of 7-nitroquinazolin-4-one (1.15g, 6.02mmol) in methanol(150mL). The resulting black mixture was degassed, flushed with hydrogen and allowed to stir for 4 hours. The mixture was filtered through celite, washed well with methanol, and the filtrate concentrated to give a tanned solid. This was purified by column chromatography (silica) using 10% methanol/ethyl acetate as the eluent. Combined fractions gave a beige solid (949mg, 98% yield).

^{1}H nmr; 6.68 (s, 1H), 6.87 (d, 1H), 7.73 (d, 1H), 7.83 (s, 1H), 11.40 (bs, 1H).

(c) Synthesis of 7-Hydroxyquinazolin-4-one

A solution of sodium nitrite(1.40g, 20.32mmol) in water (17mL) was added dropwise to a cooled suspension of 7-aminoquinazolin-4-one (712mg, 4.42mmol) in sulfuric acid/water (4.4mL, 18mL), keeping the temperature at approx. 0°C. The mixture was stirred at room temperature for 2 hours, diluted with water (15mL) and heated at reflux for 15minutes. The cooled mixture was neutralised and the precipitate was collected via filtration, and purified by column chromatography (silica) using 10% methanol/ethyl acetate as the eluent. The combined fractions gave an orange solid (541mg, 76%).

^{1}H nmr; 6.85-6.91 (m, 2H), 7.87 (s, 1H), 7.92 (s, 1H).

(d) Synthesis of 7-Hydroxy-4-ethoxyquinazoline

A mixture of 7-hydroxyquinazolin-4-one (105mg, 648 μmol), phosphorous oxychloride (2ml), and dimethylaniline (85μl, 671μmol) was heated at reflux for 15 minutes in an argon atmosphere. The cooled mixture was concentrated under vacuum, and kept in an argon atmosphere to avoid hydrolysis. This residue was dissolved in ethanol (anhydrous, 3mL), and a solution of sodium (283mg, 12.34 mmol) in ethanol (3ml) was added dropwise. The resulting yellow mixture was stirred at room temperature under argon for 2 hours, acidified to pH 6 using NaH_2PO_4 and extracted with ethyl acetate (3 x 50mL). The combined extracts were dried ($MgSO_4$), filtered and concentrated. The white solid (156mg) was used without further purification.

^{1}H nmr; 1.49 (t, 3H), 4.78 (q, 2H), 7.26 (d, 1H), 7.43 (s, 1H), 8.11 (d, 1H), 8.83 (s, 1H).

(e) Preparation of Compound No. 51

A mixture of 3-[4-(2-chloroethyl)-1-piperidinyl]-6-methyl pyridazine (76mg, 318μmol), 7-hydroxy-4-ethoxyquinazoline (100mg, 526μmol), potassium carbonate (109mg, 789μmol) and potassium iodide (53mg, 319μmol) in DMF (5mL) was heated at 90°C overnight in an argon atmosphere. The mixture was concentrated, and the residue partitioned between

ethyl acetate (100mL), and water (20mL). The organic phase was dried ($MgSO_4$), filtered, concentrated and purified by column chromatography (silica), using gradient elution (ethyl acetate – methanol/EA). The combined fractions gave a white solid (22mg, 18%). The ^1H nmr data are recorded in Table 6 below.

Example 14

Compounds No 54 and 55 were prepared by reacting 3-[4-(2-chloroethyl)-1-piperidinyl]-6-methyl pyridazine with the appropriate 6-hydroxyquinazoline following similar conditions to those described in Example 13, part (e). The ^1H nmr and/or MS data are recorded in Table 6 below.

Example 15 Preparation of 6-{2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethoxy}-2-ethoxy-quinoxaline (Compound 43 from Table 4)

(a) Preparation of 2-chloro-6-hydroxyquinoxaline

Aluminium trichloride (85mg, 638μmol) was added as a single portion to a stirred mixture of 2-chloro-6-methoxyquinoxaline (73mg, 375μmol) and anhydrous toluene (3ml) under an Argon atmosphere. The reaction mixture was heated at reflux for approx. 1 hr, then allowed to stir overnight at room temperature. Tlc (silica; 2:1 hexane/ethyl acetate) showed no remaining starting material and new polar material. Water (1ml) and ice was added and the mixture stirred. The contents were partitioned between water (5ml) and ethyl acetate (100ml). The aqueous phase was extracted into ethyl acetate (50ml), then the organic extracts combined and washed with water (10ml), followed by brine (10ml) and dried (Na_2SO_4). Concentration gave a brown solid, which was pre-adsorbed onto silica, then chromatographed on silica (9g); eluent: 20% ethyl acetate in hexane then 25% ethyl acetate in hexane to give 2-chloro-6-hydroxyquinoxaline 54mg (79%).

(b) Preparation of 2-chloro-6-{2-[1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethoxy}-quinoxaline

A mixture of 2-chloro-6-hydroxyquinoxaline (52mg, 288μmol), 3-[-4-(2-chloroethyl)-1-piperidinyl]-6-methyl pyridazine (76mg, 317μmol), potassium iodide (53mg, 317μmol) and potassium carbonate (199mg, 1.44mmol) in anhydrous dimethylformamide (2ml) was heated at 90° under an Argon atmosphere for 2 days. Tlc (silica; ethyl acetate) showed new polar material. Removal of the solvent under high vacuum and then chromatography on silica (5g; eluent: 30% hexane in ethyl acetate) gave the product as a white solid 68mg (61%).

(c) Preparation of Compound 43

Sodium (78mg, 3.39mmol) was added portionwise to anhydrous ethanol (2ml). The resulting sodium ethoxide solution was added to a stirred solution of the chloroquinoxaline from part (b) (65mg, 169μmol) in anhydrous tetrahydrofuran (2ml) under an Argon atmosphere. The reaction mixture was heated at reflux for several hours then allowed to stir at room temperature overnight. The reaction mixture was quenched with saturated ammonium chloride solution (1ml), then the contents partitioned between water (3ml) and dichloromethane (50ml). The aqueous phase was extracted into dichloromethane (50ml), the organic extracts combined and washed with brine then dried (Na_2SO_4). The crude product was pre-adsorbed onto silica then chromatographed on silica (11g; eluent 2:1 ethyl acetate/hexane) to give Compound 43 as a white solid (57mg 86%).

Example 16

Compounds No 44, 45 and 46 were prepared by reacting 3-[4-(2-chloroethyl)-1-piperidinyl]-6-methyl pyridazine or 2-[-1-(6-methyl-3-pyridazinyl)-4-piperidinyl]ethanol with the appropriate 6-hydroxyquinoxaline following similar conditions to those described in earlier examples. The ^1H nmr and/or MS data are recorded in Table 6 below.

Example 17

The compounds of the invention which are listed in Tables 1 to 5 were generally purified by chromatography on silica gel and were isolated as solids and characterised by ^{1}H nmr and mass spectroscopy. For convenience the nmr and ms data are recorded in Table 6 below.

Table 6

Compound No.	MS data (ESI)	NMR data: Proton Chemical Shift d in ppm ($CDCl_3$ unless otherwise noted)
19	415 $(M+1)^+$	1.35 (m, 1H), 1.49 (t, 3H), 1.80-1.90 (m, 6H), 2.64 (s, 3H), 2.99 (m, 2H), 3.34 (q, 2H), 4.10 (t, 2H), 4.37 (m, 2H), 6.93 (dd, 1H), 7.05 (d, 1H), 7.21 (d, 1H), 7.38 (s, 1H), 7.59 (d, 1H).
20	413 $(M+1)^+$	1.05 (t, 3H), 1.33 (m, 1H), 1.88 (m, 8H), 2.79 (s, 3H), 3.10 (m, 2H), 4.07 (t, 2H), 4.40 (m, 2H), 4.50 (t, 2H), 6.84 (dd, 1H), 7.22 (s, 1H), 7.25 (d, 1H), 7.42 (d, 1H), 7.48 (m, 1H)
21	399 $(M+1)^+$	1.33 (m, 1H), 1.48 (t, 3H), 1.79 (m, 2H), 1.92 (m, 4H), 2.73 (s, 3H), 3.04 (m, 2H), 4.07 (t, 2H), 4.39 (m, 2H), 4.60 (q, 2H), 6.84 (dd, 1H), 7.22 (s, 1H), 7.25 (d, 1H), 7.36 (d, 1H), 7.48 (d, 1H)
22	Not recorded	1.35 (m, 1H), 1.49 (t, 3H), 1.80-1.90 (m, 6H), 2.58 (s, 3H), 2.99 (m, 2H), 3.32 (q, 2H), 4.05 (t, 2H), 4.37 (m, 2H), 6.85 (dd, 1H), 6.95 (d, 1H), 7.1 (m, 2H), 7.35 (d, 1H).
23	Not recorded	1.35 (m, 1H), 1.53 (t, 3H), 1.80-1.90 (m, 6H), 2.58 (s, 3H), 2.99 (m, 2H), 4.05 (t, 2H), 4.37 (m, 2H), 4.60 (q, 2H), 6.76 (dd, 1H), 6.95 (d, 1H), 7.0-7.1 (m, 2H), 7.15-7.25 (m, 2H).
24	412 $(M+1)^+$	1.01 (t, 3H), 1.35 (m, 3H), 1.68-1.88 (m, 6H), 2.54 (s, 3H), 2.92 (m, 2H), 3.37 (t, 2H), 4.02 (t, 2H), 4.33 (m, 2H), 6.87-6.92 (m, 2H), 7.08 (d, 1H), 7.12 (s, 1H), 7.42 (d, 1H)
25	398 $(M+1)^+$	1.31 (m, 1H), 1.39-1.42 (2x t, 3H), 1.68-1.85 (m, 6H), 2.52 (s, 3H), 2.90 (m, 2H), 3.27-3.43 (2 x q, 2H), 4.02-4.14 (m, 2H), 4.25 (m, 2H), 6.75-6.85 (m, 1-2H), 6.95-7.21 (m, 3H)
26	Not recorded	0.98 (t, 3H); 1.25-1.55 (m, 3H), 1.80-1.95 (m, 6H), 2.61 (s, 3H), 2.85-3.0 (m, 4H), 4.06 (t, 2H), 4.37 (m, 2H), 6.88 (dd, 1H), 6.95-7.05 (m, 2H), 7.17 (d, 1H), 7.54 (d, 1H)
27	Not recorded	1.06 (t, 3H); 1.35 (m, 1H), 1.80-1.95 (m, 8H), 2.61 (s, 3H), 2.85-3.0 (m, 4H), 4.06 (t, 2H), 4.37 (m, 2H), 6.88-6.94 (m, 2H), 7.03 (d, 1H), 7.10 (d, 1H), 7.54 (d, 1H)
28	Not recorded	1.25-1.35 (m, 2H), 1.50 (t, 3H), 1.73-1.88 (m, 5H), 2.23 (s, 3H), 2.54 (s, 3H), 2.90 (t, 2H), 4.03 (t, 2H), 4.32-4.37 (m, 2H), 4.58 (q, 2H), 6.78-6.83 (m, 2H), 6.93 (fd, 1H), 7.32 (d, 1H)
29	Not recorded	1.25-1.27 (m, 2H), 1.39 (t, 3H), 1.76-1.91 (m, 5H), 2.42 (s, 3H), 3.18 (t, 2H), 3.89-3.93 (m, 2H), 4.01 (t, 2H), 4.57 (q, 2H), 6.82 (dd, 1H), 6.92 (fd, 1H), 7.33 (d, 1H)

30	398 $(M+1)^+$	1.24-1.29 (m, 2H), 1.49 (t, 3H), 1.75-1.86 (m, 5H), 2.33 (s, 3H), 2.46 (s, 3H), 2.92 (t, 2H), 4.03 (t, 2H), 4.58 (q, 2H), 4.78-4.83 (m, 2H), 6.81 (dd, 1H), 6.92 (fd, 1H), 7.33 (d, 1H)
31	373 $(M+1)^+$	1.46-1.52 (m, 5H), 1.78-1.90 (m, 5H), 3.03 (t, 2H), 3.55-3.59 (m, 2H), 3.85 (s, 3H), 4.03 (t, 2H), 4.50 (q, 2H), 6.79 (dd, 1H), 6.91 (bd, 1H), 7.32 (d, 1H)
32	Not recorded	1.39-1.43 (m, 2H), 1.50 (t, 3H), 1.77-2.00 (m, 5H), 2.36 (s, 3H), 3.08-3.14 (m, 2H), 4.01 (t, 2H), 4.45-4.49 (m, 2H), 4.57 (q, 2H), 6.79 (dd, 1H), 6.91 (bd, 1H), 6.98 (s, 1H), 7.35 (d, 1H)
33	Not recorded	1.27-1.34 (m, 2H), 1.51 (s, 3H), 1.73-1.88 (m, 5H), 2.24 (s, 3H), 2.94 (t, 2H), 4.02 (t, 2H), 4.37-4.42 (m, 2H), 4.58 (q, 2H), 6.72 (bs, 1H), 6.83 (dd, 1H), 6.91 (fd, 1H), 7.33 (d, 1H), 8.39 (bs, 1H).
34	Not recorded	1.45-1.55 (m, 5H), 1.69-1.82 (m, 4H), 2.23 (s, 3H), 2.72 (t, 2H), 3.93 (t, 2H), 4.57 (q, 2H), 5.79 (s, 1H), 6.77 (dd, 1H), 6.89 (fd, 1H), 7.31 (d, 1H)
35	383 $(M+1)^+$	1.34 (m, 1H); 1.50 (t, 3H); 1.80-1.95 (m, 6H); 2.74 (s, 3H); 3.05 (m, 2H); 4.08 (t, 2H); 4.40 (m, 2H); 4.46 (q, 2H); 6.85 (m, 2H); 7.24 (bd, 1H); 7.37 (bd, 1H); 7.47 (d, 1H)
36	367 $(M+1)^+$	1.34 (m, 2H), 1.43 (t, 3H), 1.82-1.94 (m, 5H), 2.74 (s, 3H), 2.96 (q, 2H), 3.05 (m, 2H), 4.10 (t, 2H), 4.40 (m, 2H), 6.89 (dd, 1H), 6.97 (fd, 1H), 7.22 (d, 1H), 7.35 (d, 1H), 7.50 (d, 1H)
37	403 $(M+1)^+$	1.37 (m, 1H), 1.50 (t, 3H), 1.91 (m, 4H), 3.03 (bt, 2H), 4.08 (t, 2H), 4.39 (bd, 2H), 4.46 (q, 2H), 6.82-6.86 (m, 2H), 6.97 (bd, 1H), 7.21 (bd, 1H), 7.47 (d, 1H)
38	397 $(M+1)^+$	1.06 (t, 3H), 1.34 (m, 3H), 1.81-1.97 (m, 6H), 2.72 (s, 3H), 3.12 (m, 2H), 4.08 (t, 2H), 4.36 (t, 2H), 6.84 (m, 2H), 7.24 (m, 1H), 7.41-7.49 (m, 2H)
39	381 $(M+1)^+$	1.03 (t, 3H), 1.35 (m, 2H), 1.81-1.94 (m, 7H), 2.69 (s, 3H), 2.90 (t, 2H), 3.03 (t, 2H), 4.10 (t, 2H), 4.36 (m, 2H), 6.89 (bd, 1H), 6.96 (s, 1H), 7.14 (bd, 1H), 7.29 (bd, 1H), 7.49 (bd, 1H)
40	399 $(M+1)^+$	1.36 (m, 2H), 1.48 (t, 3H), 1.79-1.91 (m, 5H), 2.60 (s, 3H), 2.97 (dt, 2H), 4.11 (t, 2H), 4.36 (m, 2H), 4.56 (q, 2H), 6.95 (dd, 1H), 6.99 (bd, 1H), 7.14 (fd, 1H), 7.16 (bd, 1H), 7.76 (bd, 1H)
41	Not recorded	1.30-1.34 (m, 2H), 1.48 (t, 3H), 1.60-1.70 (m, 1H), 1.84-1.91 (m, 4H), 3.04 (t, 2H), 4.01 (t, 2H), 4.39-4.49 (m, 4H), 6.82-6.86 (m, 2H), 6.99 (d, 1H), 7.23 (d, 1H), 7.47 (d, 1H)
42	384 $(M+1)^+$	1.43 (t, 3H), 2.46 (s, 3H), 2.76 (t, 4H), 2.93 (t, 2H), 3.62 (t, 4H), 4.18 (t, 2H), 4.38 (q, 2H), 6.8 (m, 2H), 6.89 (d, 1H), 7.09 (d, 1H), 7.42 (d, 1H)
43	Not recorded	1.37 (m, 1H), 1.46 (t, 3H), 1.85-1.92 (m, 6H), 2.66 (s, 3H), 3.01 (t, 2H), 4.16 (t, 2H), 4.38 (m, 2H), 4.51 (q, 2H), 7.08 (bd, 1H), 7.22-7.26 (m, 1H), 7.32 (m, 1H), 7.34 (fd, 1H), 7.72 (d, 1H), 8.40 (s, 1H)
44	418 $(M+1)^+$	1.37 (m, 1H), 1.86-1.96 (m, 6H), 2.74 (s, 3H), 3.06 (t, 2H), 4.19 (t, 2H), 4.41 (m, 2H), 7.22 (bd, 1H), 7.29 (fd, 1H), 7.35 (bd,

		1H), 7.43 (dd, 1H), 7.91 (d, 1H)
45	Not recorded	1.36 (m, 1H), 1.50 (2 x t, 6H), 1.80-1.94 (m, 6H), 2.68 (s, 3H), 3.02 (m, 2H), 4.13 (t, 2H), 4.38 (m, 2H), 4.59 (2 x q, 4H), 7.09 (dd, 1H), 7.11-7.15 (m, 1H), 7.15 (fd, 1H), 7.27 (bd, 1H), 7.62 (d, 1H)
46	394 $(M+1)^+$	1.37 (m, 2H), 1.47 (t, 3H), 1.82-1.95 (m, 5H), 2.69 (s, 3H), 3.03 (m, 2H), 4.18 (t, 2H), 4.39 (m, 2H), 4.52 (q, 2H), 7.13 (bd, 1H), 7.15 (s, 1H), 7.15-7.19 (m, 1H), 7.27 (bd, 1H), 7.87 (d, 1H), 8.29 (s, 1H)
47	Not recorded	1.50 (t, 3H), 1.55-1.89 (m, 5H), 2.99 (t, 2H), 3.96 (t, 3H), 4.35-4.39 (m, 2H), 4.56 (q, 2H), 6.79 (dd, 1H), 6.91-6.96 (m, 2H), 7.21 (d, 1H), 7.35 (d, 1H)
48	384 $(M+1)^+$	1.49 (t, 3H), 2.54 (s, 3H), 2.81 (m, 4H), 2.95 (t, 2H), 3.71 (m, 4H), 4.21 (t, 2H), 4.58 (q, 2H), 6.84 (dd, 1H), 6.86 (d, 1H), 6.95 (fd, 1H), 7.09 (bd, 1H), 7.34 (bd, 1H)
49	Not recorded	1.46-1.57 (m, 5H), 1.73-1.85 (m, 4H), 2.25 (s, 3H), 2.73 (t, 2H), 3.99 (t, 2H), 4.45 (q, 2H), 5.80 (s, 1H), 6.81-6.84 (m, 2H), 7.43 (d, 1H).
50	Not recorded	1.42-1.44 (m, 2H), 1.49 (t, 3H), 1.79-1.86 (m, 5H), 2.56 (s, 3H), 3.08-3.15 (m, 2H), 3.91-3.94 (m, 2H), 4.06 (t, 2H), 4.45 (q, 2H), 6.82-6.85 (m, 2H), 7.45 (d, 1H)
51	Not recorded	1.22-1.37 (m, 2H), 1.48 (t, 3H), 1.51-1.88 (m, 3H), 2.53 (s, 3H), 2.93 (t, 2H), 4.14 (t, 2H), 4.31-4.35 (m, 2H), 4.59 (q, 2H), 6.88 (d, 1H), 7.06 (d, 1H), 7.13 (d, 1H), 7.22 (d, 1H), 8.04 (d, 1H), 8.69 (s, 1H)
52	394 $(M+H)^+$	(CD_3OD) 1.4 (m, 2H); 1.62 (t, 3H); 1.93 (m, 5H); 2.51 (s, 3H); 2.99 (m, 2H); 4.35 (m, 4H); 4.52 (q, 2H); 7.24 (d, 1H); 7.31 (d, 1H); 7.47 (dd, 1H); 7.64 (d, 1H); 8.19 (d, 1H) and 8.99 (br s 1H)
53	394 $(M+H)^+$	(CD_3OD) 1.3 (m, 2H); 1.62 (t, 3H); 1.93 (m, 5H); 2.51 (s, 3H); 2.99 (m, 2H); 4.32 (m, 2H); 4.38 (m, 2H); 4.52 (q, 2H); 7.23 (d, 1H); 7.31 (d, 1H); 7.47 (d, 1H); 7.58 (dd, 1H); 8.27 (d, 1H) and 8.95 (br s 1H)
54	Not recorded	1.31-1.43 (m, 2H), 1.52 (t, 3H), 1.82-1.91 (m, 3H), 2.55 (s, 3H), 2.95 (t, 2H), 4.16 (t, 2H), 4.32-4.37 (m,2H), 4.65 (q, 2H), 6.87-6.93 (m, 1H), 7.05-7.11 (m, 1H), 7.39 (s, 1H), 7.45 (d, 1H), 7.84 (d, 1H), 8.67 (s, 1H)
55	Not recorded	1.29-1.33 (m, 2H), 1.42-1.53 (m, 6H), 1.78-1.89 (m, 5H), 2.52 (s, 3H), 2.93 (t, 2H), 4.08-4.14 (m, 2H), 4.31-4.35 (m, 2H), 4.44 (q, 2H), 4.63 (q, 2H), 6.89 (d, 1H), 7.06 (d, 1H), 7.32-7.37 (m, 2H), 7.58 (d, 1H)
56	384 $(M+1)^+$	1.34-1.38 (m, 2H), 1.36 (t, 3H), 1.79-1.89 (m, 5H), 2.59 (s, 3H), 2.96 (dt, 2H), 4.02 (q, 2H), 4.08 (t, 2H), 4.36 (m, 2H), 6.64 (fd, 1H), 6.81 (dd, 1H), 6.98 (bd, 1H), 7.15 (bd, 1H), 7.67 (d, 1H)
57	397 $(M+1)^+$	0.98 (t, 3H), 1.35 (m, 2H), 1.78-1.96 (m, 7H), 2.78 (s, 3H), 3.08 (t, 2H), 3.95 (t, 2H), 4.09 (t, 2H), 4.41 (m, 2H), 6.64 (fd, 1H),

		6.81 (dd, 1H), 7.50 (bd, 1H), 7.41 (bd, 1H), 7.69 (d, 1H)
58	Not recorded	0.96 (t, 3H), 1.4 (m, 3H), 1.68-1.88 (m, 6H), 2.11 (q, 2H), 2.52 (s, 3H), 2.92 (m, 2H), 4.06 (t, 2H), 4.33 (m, 2H), 4.60 (t, 2H), 6.86 (d, 1H), 7.0-7.1 (m, 3H), 7.08 (d, 1H), 7.70 (d, 1H)

Example 15

Anti-HRV activity in mammalian cell culture assays

Inhibition of viral cytopathic effect (CPE) and measurement of cytotoxicity

The ability of compounds to suppress virus replication and thereby protect cells from HRV-induced CPE was measured using human embryo lung (MRC-5cells infected with HRV type 1A. Cells grown in 96 well tissue culture plates using conventional mammalian tissue culture medium (such as minimum essential medium) supplemented with fetal calf serum were used in an assay essentially similar to that described by Sidwell and Huffman (Applied Microbiology, 22, 797-801 (1971)). Test compounds were dissolved in 100% anhydrous dimethyl sulfoxide and serially diluted in tissue culture medium. The antiviral potency of the test compounds was assessed by exposing replicate tissue culture wells to a selected dilution series of between 6 and 7 compound concentrations in the presence of sufficient test virus to invoke significant CPE over the course of the assay. Control cells were also exposed to identical concentrations of compounds in the absence of virus or were infected with virus under the same conditions but in the absence of compounds. Compounds of established anti-HRV efficacy (enviroxime, ribavirin and pirodavir) were assayed by identical procedures in parallel to the test compounds. Tissue culture media were identically supplemented to maintain cell viability and support viral growth while suppressing bacterial growth over the period of the assay (supplements: 2% fetal calf serum, 0.01% sodium bicarbonate, 50 µg/ml gentamicin, 5 µM magnesium chloride, 10 mM of zinc chloride). The assays were incubated at 37°C in a 5% CO_2 atmosphere until significant CPE was observed by microscopic examination of the untreated, HRV infected control cells (generally between 5 and 8 days). At this time all infected cultures were examined by eye using a light microscope and CPE scored on a scale of 0 (no CPE) to 4 (maximum CPE). Uninfected treated cultures were similarly scored for cytotoxic effects (*eg.* cell enlargement, granularity, rounding, detachment). These scores were used to

generate EC_{50} (concentration of compound yielding 50% antiviral efficacy) and CC_{50} (concentration of compound yielding 50% cytotoxicity) values by line regression analysis from plots of compound concentration versus % CPE or % cytotoxicity, respectively. As an alternative to a CC_{50} value, cytoxicity in some cases was expressed as the Minimum Toxic Concentration (MTC). The MTC corresponds to the lowest compound concentration at which cytotoxic effects were observed.

In some cases the visual scoring system described above was validated by vital dye staining to measure cell viability. The vital dye technique used was a modification of the method described by McManus (Appl. Environment. Microbiol., 31, 35-38, 1976). After the assay had been scored by eye with the aid of a microscope, 100 µl of neutral red (NR) solution (0.34% NR in phosphate buffered saline (PBS)) was added to each well and mixed gently. The assays were returned to the 37°C incubator for 2 hours to facilitate uptake of the NR by viable cells. The medium/NR mixture was then aspirated from the surface of the cells, which were washed twice with PBS. 0.25 ml of absolute ethanol containing Sorensen's citrate buffer I, was added with gentle mixing and the assays incubated at room temperature in the dark for 30 minutes to dissolve the NR. NR staining of viable cells was then quantified spectrophotometrically by measuring the colour density of the NR solution using a BioTek EL-309 microplate reader at dual wavelengths of 540 and 405 nm. The differences in the two readings were automatically determined to eliminate background errors. EC_{50} and CC_{50} values were determined by regression analysis matching compound concentration to NR staining.

The results are shown in the Tables 7 and 8 below. Selectivity indices (SI) are the CC_{50} or MTC divided by the EC_{50}. Tables 7 and 8 also show IC_{50} data for the testing of the compounds of the invention against HRV strains 2 and 14. These results were obtained using a similar CPE method to that described above for HRV1A.

Table 7

Compound No	IC_{50} (μg/ml)		IC_{50} (μg/ml)	
	HRV1A	CC_{50}	HRV2	HRV14
1	0.179	>1	>0.50	>0.50
2	0.120	>1	>0.50	>0.50
3	0.060	>1	0.144	0.130
4	0.006	>1	0.099	0.047
5			0.003	0.007
6			0.067	0.146
7			0.002	0.006
8			0.008	0.020
9			0.061	0.056
10			0.065	0.056
11			0.002	0.020
12			0.159	0.099
13			0.004	0.015
14			0.024	0.006
15			0.007	0.006

Table 8

Compound No	IC_{50} (μg/ml)	
	HRV2	HRV14
16	0.10	0.169
19	0.165	0.049
20	0.166	0.041
21	0.104	0.014
22	0.004	0.050
23	0.045	-
24	0.131	>0.250
26	0.130	0.082
27	0.075	0.028
28	0.101	0.040
30	>0.250	0.198

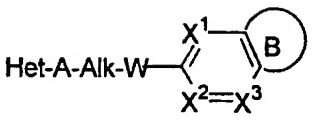
31	0.237	>0.250
32	0.012	0.039
33	0.167	0.166
34	0.209	0.118
35	0.001	0.005
36	0.024	0.088
37	0.003	0.019
38	0.003	0.029
39	0.084	0.013
40	0.003	0.029
41	0.003	0.009
43	0.012	0.012
46	0.084	0.013
47	0.004	0.010
48	0.069	0.011
49	0.035	0.012
50	0.007	0.005
51	0.027	0.120
52	0.190	0.200
56	0.246	>0.250
57	0.133	0.237
58	0.032	0.139

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations of any two or more of said steps or features.

THE CLAIMS:

1. A compound of formula I

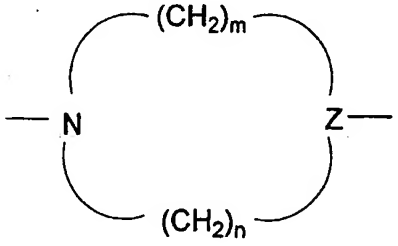


I

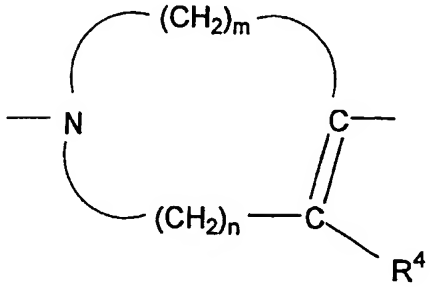
its salts, and pharmaceutically acceptable derivatives thereof where

Het is an optionally substituted 5- or 6-membered monocyclic heterocyclic radical or an optionally substituted 9- or 10-membered bicyclic heterocyclic radical;

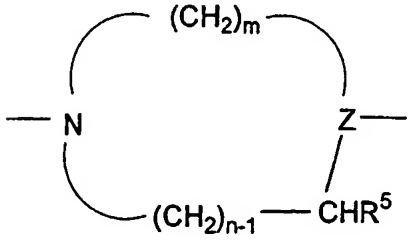
A is O, S, NH, N(C_{1-6}alkyl), CH_2O, a direct bond or a bivalent heterocyclic radical of the formula



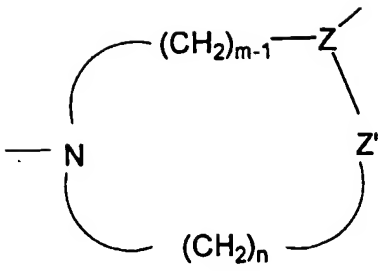
(b-1)



(b-2),



(b-3), or



(b-4)

where one or more of the carbon atoms within the radicals (b-1) to (b-4) may be optionally substituted with C_{1-6}alkyl or two carbon atoms in the radicals (b-1) to (b-4) may be bridged with a C_{2-4}alkylene radical, m and n are each independently integers of 1 to 4 inclusive with the proviso that the sum of m and n in radicals (b-1) to (b-4) is 3, 4 or 5;

Z is N or CR^6 where R^6 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino;

Z′ is O, S, CHR^7 or NR^8 where R^7 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino and R^8 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl; and

R^5 is hydrogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

Alk is C_{1-7}alkylene or a direct bond;

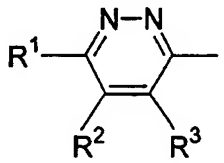
W is O, S, OCH_2, a direct bond or NR^9 where R^9 is hydrogen or C_{1-6}alkyl;

X^1, X^2 and X^3 are each independently selected from N and CR, where R is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy and

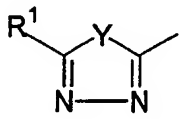
B is a five or six membered unsaturated heterocyclic ring, substituted with at least one substituent selected from , R^{10}, OR^{10}, SR^{10} and NR^9R^{10} where R^{10} is C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkenyl, haloC_{1-6}alkenyl, C_{1-6}alkynyl or haloC_{1-6}alkynyl,

with the proviso that when Alk is a direct bond and A is O, S, CH_2O or a direct bond, then W is not O, S, OCH_2 or a direct bond.

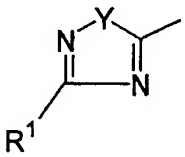
2. A compound according to claim wherein Het is a radical selected from



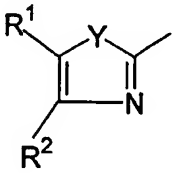
(a-1)



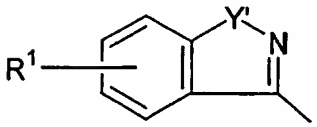
(a-2)



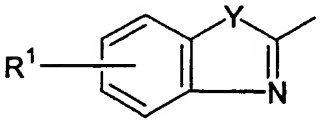
(a-3)



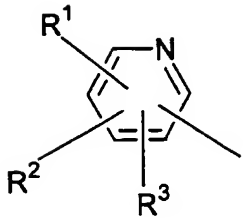
(a-4)



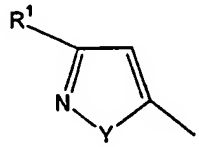
(a-5)



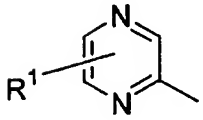
(a-6)



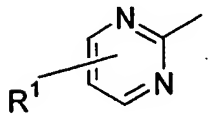
(a-7)



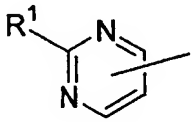
(a-8)



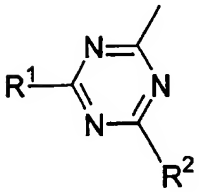
(a-9)



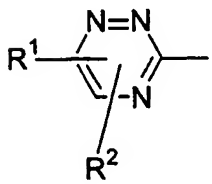
(a-10)



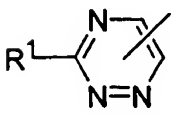
(a-11)



(a-12)



(a-13)



(a-14)

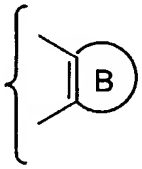
wherein R^1 is hydrogen, C_{1-6} alkyl, halo, hydroxy, mercapto, haloC_{1-6}alkyl, amino, mono or di(C_{1-6}alkyl)amino, cyano, formyl, C_{1-6}alkoxy, hydroxyC_{1-4} alkyl, C_{1-4}alkoxyC_{1-4} alkyl, C_{1-6}haloalkoxy, aryloxy, C_{1-6}alkylthio, arylthio, C_{1-6}alkylsulphinyl, C_{1-6}alkylsulphonyl, arylsulphinyl, arylsulphonyl, -CH=NO-C_{1-4}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonyl or aryl;

R^2 and R^3 are each independently selected from hydrogen, C_{1-6}alkyl, C_{1-6}alkoxy, halo or, in radicals (a-1), (a-4), (a-7) and (a-13), R^1 and R^2, or R^2 and R^3 combined may represent a bivalent radical of formula -CH=CH-CH=CH- or $(CH_2)_p$ where p is an integer from 2 to 4;

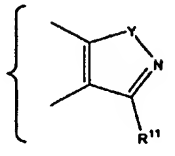
Y is O or S; and

Y′ is O, S, SO or SO_2.

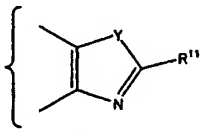
3. A compound according to claim wherein



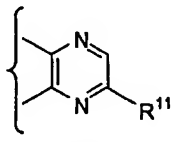
is selected from



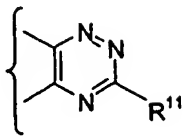
(c-1)

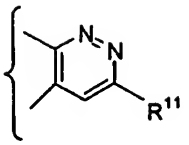


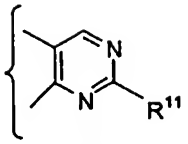
(c-2)

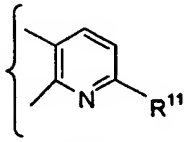


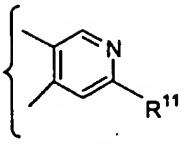
(c-3)

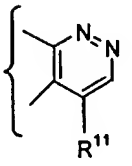

(c-4)

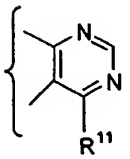

(c-5)

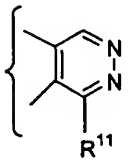

(c-6)


(c-7)


(c-8)


(c-9)


(c-10)


(c-11)

where Y is O, S or NR^9; and R^{11} is R^{10}, OR^{10}, SR^{10} or NR^9R^{10}, where R^9 and R^{10} are as defined in claim 1.

4. A compound according to claim 2 where Het is a radical of formula (a-1), (a-2) or (a-8).

5. A compound according to claim 2 wherein R^1 is selected from hydrogen, methyl, ethyl, chloro, methoxy and trifluoromethyl.

6. A compound according to claim 2 wherein R^2 and R^3 are independently hydrogen, chloro or methyl.

7. A compound according to claim 2 wherein Y is O or S.

8. A compound according to claim 1 wherein A is O, NH, NMe, a direct bond or a radical of formula (b-1).

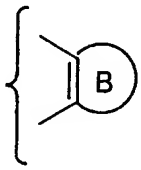
9. A compound according to claim 1 wherein Z is CH or N.

10. A compound according to claim 1 wherein Alk is C_{1-6}alkylene or a direct bond.

11. A compound according to claim 1 wherein W is O.

12. A compound according to claim 1 wherein X^1, X^2 and X^3 are each CH.

13. A compound according to claim 3 wherein

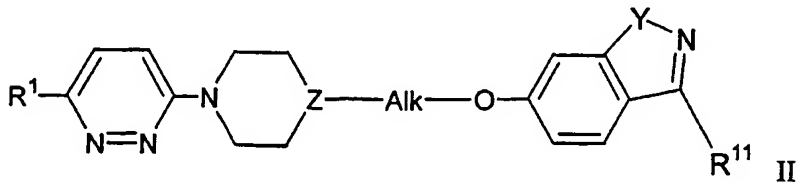


is a radical of formula (c-1) or (c-2).

14. A compound according to claim 3 wherein in (c-1) to (c-11) R^{11} is selected from methyl, ethyl, n-propyl, n-butyl, methoxy, ethoxy, n-propoxy, methylthio, ethylthio, n-propylamino and chloro.

15. A compound according to claim 3 wherein in (c-1) or (c-2) Y is O or S.

16. A compound of formula II:



II

wherein:

R^1 is hydrogen, C_{1-4}alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4} alkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

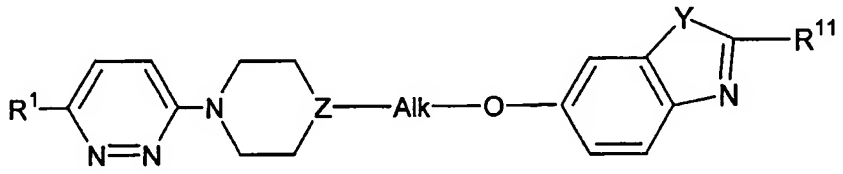
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

17. A compound of formula III:



III

wherein:

R^1 is hydrogen, C_{1-4}alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4} alkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

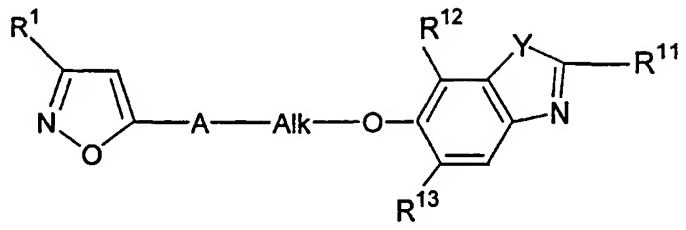
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

18. A compound of formula IV:



IV

wherein:

R^1 is hydrogen, C_{1-4}alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkoxyC_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

A is a bond or CH_2O;

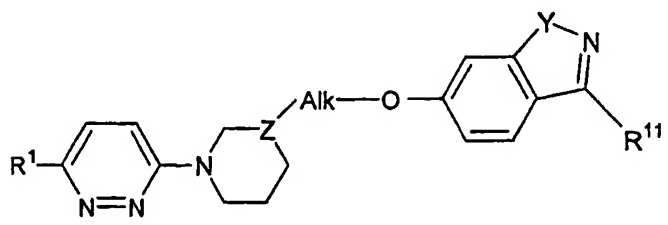
Y is O, S, NH or NMe;

Alk is C_{1-7}alkylene;

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl; and

R^{12} and R^{13} are each independently hydrogen, halogen, C_{1-4}alkyl or C_{1-4}alkoxy.

19. A compound of formula V:



V

wherein:

R^1 is hydrogen, C_{1-4} alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

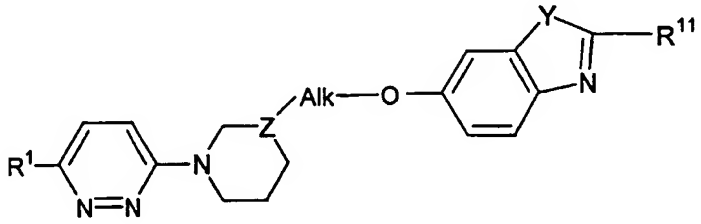
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

20. A compound of formula VI:



VI

wherein:

R^1 is hydrogen, C_{1-4} alkyl, halo, hydroxy, mercapto, trifluoromethyl, amino, mono or di(C_{1-4}alkyl)amino, cyano, formyl, -CH=NO-C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}haloalkoxy, aryloxy, C_{1-4}alkylthio, or aryl;

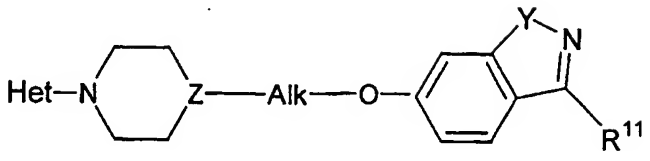
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

21. A compound of formula VII:



VII

wherein:

Het is pyridyl, pyrazinyl, thiadiazolyl, benzoxazolyl, 1,3,5-triazinyl, pyrimidinyl or quinoxalinyl, each of which may be optionally substituted with 1 to 3 substituents selected from halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy;

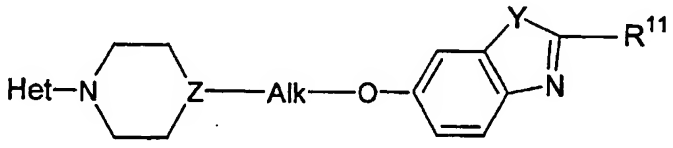
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10} where R^{10} is C_{1-4}alkyl.

22. A compound of formula VIII:



VIII

wherein:

Het is pyridyl, pyrazinyl, thiadiazolyl, benzoxazolyl, 1,3,5-triazinyl, pyrimidinyl or quinoxalinyl, each of which may be optionally substituted with 1 to 3 substituents selected from halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy;

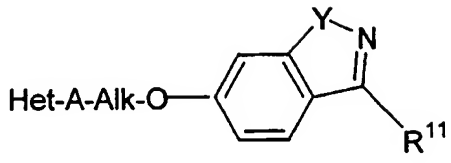
Y is O, S, NH or NMe;

Z is CH or N;

Alk is C_{1-6}alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

23. A compound of formula IX:



IX

wherein:

Het is pyridyl, pyridazinyl, pyrazinyl, thiadiazolyl, benzoxazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, pyrimidinyl or quinoxalinyl, each of which may be optionally substituted with 1 to 3 substituents selected from halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy;

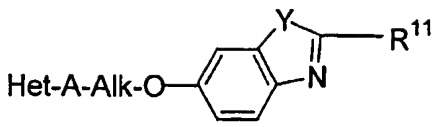
A is a direct bond, O, NH or NMe;

Y is O, S, NH or NMe;

Alk is C_{1-6} alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

24. A compound of X:



X

wherein:

Het is pyridyl, pyridazinyl, pyrazinyl, thiadiazolyl, benzoxazolyl, 1,2,4-triazinyl, 1,3,5-triazinyl, pyrimidinyl or quinoxalinyl, each of which may be optionally substituted with 1 to 3 substituents selected from halo, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy or hydroxy;

A is a direct bond, O, NH or NMe;

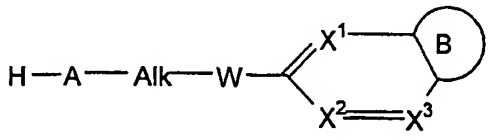
Y is O, S, NH or NMc;

Alk is C_{1-6} alkylene; and

R^{11} is OR^{10} or SR^{10}, where R^{10} is C_{1-4}alkyl.

25. A compound of formula I as described in any one of tables 1 to 5.

26. A compound of formula XI:



XI

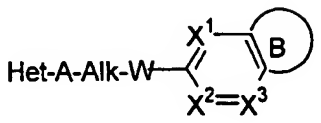
where A, Alk, W, Ar, X^1, X^2 , X^3 and B are as defined in claim 1.

27. A composition comprising a compound of formula I according to claim 1 together with a pharmaceutically acceptable carrier.

28. A composition according to claim 27 which is a pharmaceutical composition.

29. A pharmaceutical composition comprising

a compound of formula I

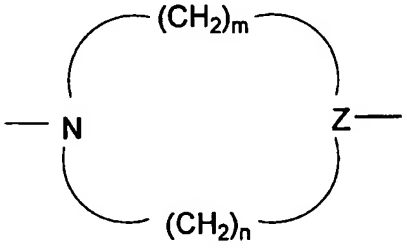


I

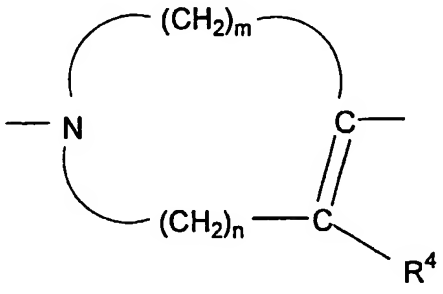
its salts, and pharmaceutically acceptable derivatives thereof where

Het is an optionally substituted 5- or 6-membered monocyclic heterocyclic radical or an optionally substituted 9- or 10-membered bicyclic heterocyclic radical;

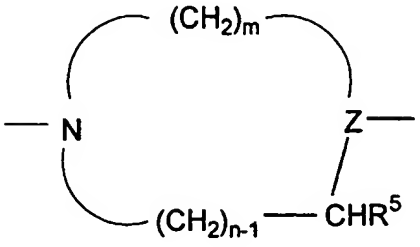
A is O, S, NH, N(C_{1-6}alkyl), CH_2O, a direct bond or a bivalent heterocyclic radical of the formula



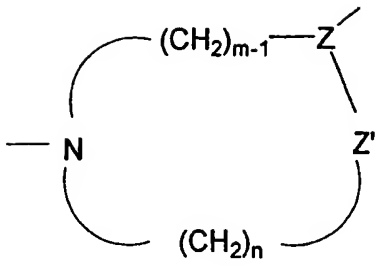
(b-1)



(b-2),



(b-3), or



(b-4)

where one or more of the carbon atoms within the radicals (b-1) to (b-4) may be optionally substituted with C_{1-6}alkyl or two carbon atoms in the radicals (b-1) to (b-4) may be bridged with a C_{2-4}alkylene radical, m and n are each independently integers of 1 to 4 inclusive with the proviso that the sum of m and n in radicals (b-1) to (b-4) is 3, 4 or 5;

Z is N or CR^6 where R^6 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino;

Z' is O, S, CHR^7 or NR^8 where R^7 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino and R^8 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl; and

R^5 is hydrogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

Alk is C_{1-7}alkylene or a direct bond;

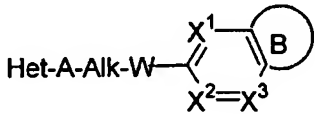
W is O, S, OCH_2, a direct bond or NR^9 where R^9 is hydrogen or C_{1-6}alkyl;

X^1, X^2 and X^3 are each independently selected from N and CR, where R is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy and

B is a five or six membered unsaturated heterocyclic ring, substituted with at least one substituent selected from , R^{10}, OR^{10}, SR^{10} and NR^9R^{10} where R^{10} is C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkenyl, haloC_{1-6}alkenyl, C_{1-6}alkynyl or haloC_{1-6}alkynyl,

with the proviso that when Alk is a direct bond and A is O, S, CH_2O or a direct bond, then W is not O, S, OCH_2 or a direct bond.

30. A method for the treatment or prophylaxis of a picornavirus infection in a mammal including the step of administering an effective amount of a compound of formula I

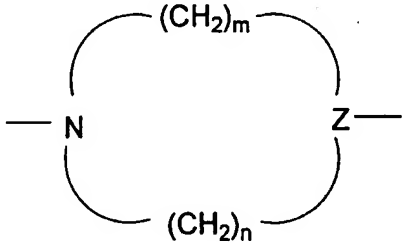


I

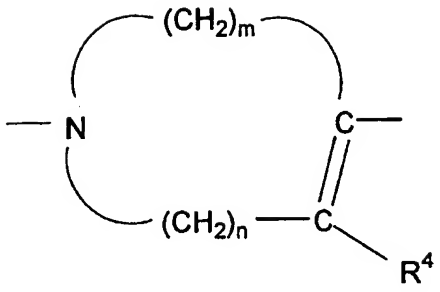
its salts, and pharmaceutically acceptable derivatives thereof where

Het is an optionally substituted 5- or 6-membered monocyclic heterocyclic radical or an optionally substituted 9- or 10-membered bicyclic heterocyclic radical;

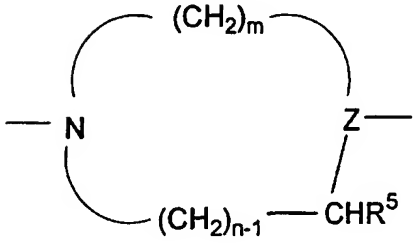
A is O, S, NH, N(C_{1-6}alkyl), CH_2O, a direct bond or a bivalent heterocyclic radical of the formula



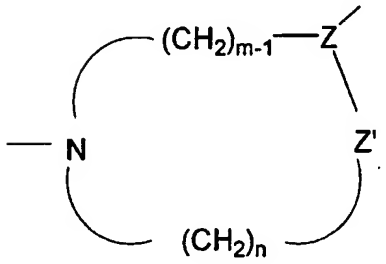
(b-1)



(b-2),



(b-3), or



(b-4)

where one or more of the carbon atoms within the radicals (b-1) to (b-4) may be optionally substituted with C_{1-6}alkyl or two carbon atoms in the radicals (b-1) to (b-4) may be bridged with a C_{2-4}alkylene radical, m and n are each independently integers of 1 to 4 inclusive with the proviso that the sum of m and n in radicals (b-1) to (b-4) is 3, 4 or 5;

Z is N or CR^6 where R^6 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino;

Z′ is O, S, CHR^7 or NR^8 where R^7 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino and R^8 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl; and

R^5 is hydrogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

Alk is C_{1-7}alkylene or a direct bond;

W is O, S, OCH_2, a direct bond or NR^9 where R^9 is hydrogen or C_{1-6}alkyl;

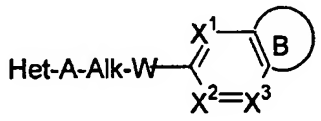
X^1, X^2 and X^3 are each independently selected from N and CR, where R is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy and

B is a five or six membered unsaturated heterocyclic ring, substituted with at least one substituent selected from R^{10}, OR^{10}, SR^{10} and NR^9R^{10} where R^{10} is C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkenyl, haloC_{1-6}alkenyl, C_{1-6}alkynyl or haloC_{1-6}alkynyl,

with the proviso that when Alk is a direct bond and A is O, S, CH_2O or a direct bond, then W is not O, S, OCH_2 or a direct bond.

31. A method of claim 29 wherein the picornaviral infection is caused by one or more serotypes of rhinovirus.

32. Use of a compound of formula I

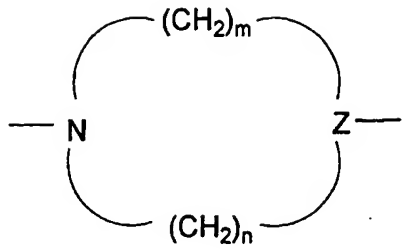


I

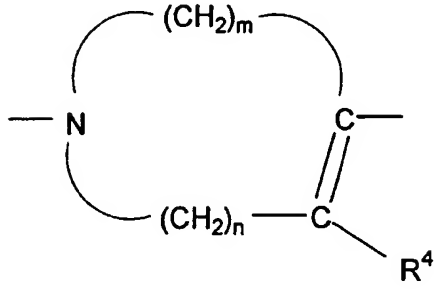
its salts, and pharmaceutically acceptable derivatives thereof where

Het is an optionally substituted 5- or 6-membered monocyclic heterocyclic radical or an optionally substituted 9- or 10-membered bicyclic heterocyclic radical;

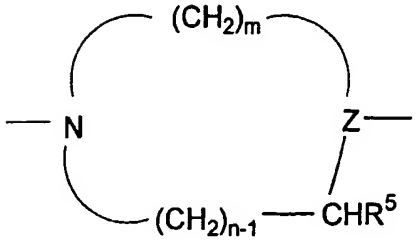
A is O, S, NH, N(C_{1-6}alkyl), CH_2O, a direct bond or a bivalent heterocyclic radical of the formula



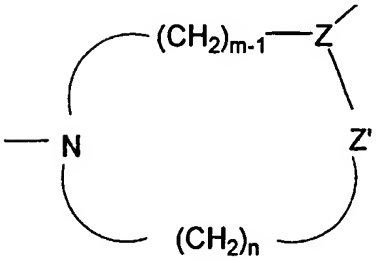
(b-1)



(b-2),



(b-3), or



(b-4)

where one or more of the carbon atoms within the radicals (b-1) to (b-4) may be optionally substituted with C_{1-6}alkyl or two carbon atoms in the radicals (b-1) to (b-4) may be bridged with a C_{2-4}alkylene radical, m and n are each independently integers of 1 to 4 inclusive with the proviso that the sum of m and n in radicals (b-1) to (b-4) is 3, 4 or 5;

Z is N or CR^6 where R^6 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino;

Z' is O, S, CHR^7 or NR^8 where R^7 is hydrogen, hydroxy, C_{1-6}alkyl, C_{1-6}alkoxy or amino and R^8 is hydrogen or C_{1-6}alkyl;

R^4 is hydrogen or C_{1-6}alkyl; and

R^5 is hydrogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy;

Alk is C_{1-7}alkylene or a direct bond;

W is O, S, OCH_2, a direct bond or NR^9 where R^9 is hydrogen or C_{1-6}alkyl;

X^1, X^2 and X^3 are each independently selected from N and CR, where R is hydrogen, halogen, hydroxy, C_{1-6}alkyl or C_{1-6}alkoxy and

B is a five or six membered unsaturated heterocyclic ring, substituted with at least one substituent selected from , R^{10}, OR^{10}, SR^{10} and NR^9R^{10} where R^{10} is C_{1-6}alkyl, haloC_{1-6} alkyl, C_{1-6}alkenyl, haloC_{1-6}alkenyl, C_{1-6}alkynyl or haloC_{1-6}alkynyl,

with the proviso that when Alk is a direct bond and A is O, S, CH_2O or a direct bond, then W is not O, S, OCH_2 or a direct bond.

33. Use according to claim 32 wherein the picornavirus infection is one caused by one or more of the serotypes of rhinovirus.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01627

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C07D 263/58, 261/20, 277/68, 275/04, 237/26, 249/18; A61K 31/416, 31/4184, 31/423, 31/428, 31/4192; A61P 31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN: File Reg, File CA, substructure, keywords

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 99/55663 A1 (VERTEX PHARMACEUTICALS INCORPORATED) 4 November 1999 See claim 1	1-15, 27-29
P,A	WO 01/38314 A1 (SMITHKLINE BEECHAM CORPORATION) 31 May 2001 See whole document	1-33
P,A	WO 01/38313 A1 (SMITHKLINE BEECHAM CORPORATION) 31 May 2001 See whole document	1-33

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
15 March 2002

Date of mailing of the international search report
25 MAR 2002

Name and mailing address of the ISA/AU

AUSTRALIAN PATENT OFFICE
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Authorized officer

IAN DOWD

Telephone No : (02) 6283 2273

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01627

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 00/78746 A1 (BIOTA SCIENTIFIC MANAGEMENT PTY LTD) 28 December 2000 See whole document	1-33
A	WO 99/59587 A1 (ELI LILLY AND COMPANY) 25 November 1999 See whole document	1-33
A	WO 98/55120 A1 (ELI LILLY AND COMPANY) 10 December 1998 See whole document	1-33
A	WO 97/46236 A1 (ELI LILLY AND COMPANY) 11 December 1997 See whole document	1-33
A	EP 435381 B1 (JANSSEN PHARMACEUTICA N.V.) 3 July 1991 See whole document	1-33
A	EP 398427 B1 (JANSSEN PHARMACEUTICA N.V.) 22 November 1990 See whole document	1-33

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01627

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :

because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : **1-33 (all in part)**

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

See supplemental sheet.

3. ☐ Claims Nos :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU01/01627

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: I part 2

The breadth of the claims encompasses a large number of compounds. A meaningful search of the whole of the claimed scope was not possible, mainly for economic reasons. Consequently the search was conducted to the extent that a substructure search was performed on a generic structure of the actual compounds exemplified in the specification. Additionally, a keyword search was performed on the alleged use of the compounds.

The applicant's attention is also drawn to the fact that claims which were not subject to an international search report need not be the subject of an international preliminary examination.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU01/01627

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
WO	9955663	AU	36651/99	EP	1076641		
WO	200138314	AU	200117832				
WO	200138313	AU	200117823				
WO	200078746	AU	200052008	EP	1187827		
WO	9959587	AU	75830/98	CZ	20004278	EP	1077701
		BR	9815899	HU	200102117	NO	20005795
WO	9855120	AU	77151/98	EP	1001767	US	6114327
WO	9746236	AU	32127/97	BR	9709643	CA	2254997
		CN	1220602	EP	914120	US	5891874
EP	435381	AU	68418/90	AU	31137/93	CA	2031889
		CN	1052857	CZ	9006401	FI	906312
		HR	930482	HU	59398	IE	904688
		IL	96770	JP	4128283	NO	905541
		NZ	236446	PH	27523	PL	288406
		PT	96361	ZA	9010357	ZW	201/90
		US	5100893	US	5196535		
EP	398427	AU	54942/90	CA	2016747	JP	3056484
		NZ	233526	PT	94036	ZA	9003667
		ZM	56/90	US	5112825		

END OF ANNEX